CASE REPORT

Tumour-associated osteomalacia and hypoglycaemia in a patient with prostate cancer: is Klotho involved?

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SUMMARY

Tumour-associated osteomalacia is a paraneoplastic syndrome caused by renal phosphate wasting, leading to severe hypophosphataemia. Excess of circulating fibroblast growth factor 23 (FGF23) is the likely cause, acting via the FGF23/ α -Klotho coreceptor, a critical regulator of phosphate metabolism. The other possible effects of that complex in humans are still under investigation. We present a case of an 84-year-old Belgian man, presenting prostate cancer with bone metastases. From June 2010 to March 2013, he presented three episodes of disease progression. From January 2012, the patient developed a progressively marked dorsal kyphosis with significant hypophosphataemia. The calculated TRP (tubular reabsorption of phosphate) was decreased and the FGF23 increased. Mid-March 2013, the patient died after a profound unconsciousness due to hypoglycaemia with hypothermia. We hypothesised that the two paraneoplastic manifestations of this patient (tumour-associated osteomalacia and refractory hypoglycaemia) were due to one cause chain with two main nodes—FGF23 and its coreceptor Klotho.

We report a case of a patient with an advanced castration-refractory prostate cancer, who developed severe hypophosphataemia with increased renal phosphate excretion. The patient also presented refractory hypoglycaemia, which was considered paraneoplastic since other causes of hypoglycaemia could be excluded.

We speculate that our patient had two related paraneoplastic syndromes: TAO and hypoglycaemia. In an Occam's Razor perspective, we hypothesised that the two paraneoplastic manifestations of our patient (TAO and hypoglycaemia) were due to one cause chain with two main nodes. High levels of FGF23 might have been the common cause of TAO and hypoglycaemia.

CASE PRESENTATION

An 84-year-old man consulted for prostatic cancer. The medical history of the patient included irritable colon, chronic gastritis, thyroid hypofunction and fracture of the femur.

There was no tobacco or alcohol use. The cancer diagnosis was made in 2009 and the patient started treatment with a luteinising hormone releasing hormone agonist. The cancer progressed in 2010 with bone metastases. Zoledronic acid and flutamide were started; 5 months later there was a new bone progression. The treatment was changed to ketoconazole. After an increase of prostate specific antigen (PSA) in November 2011, the patient received treatment with docetaxel and prednisone, which was badly tolerated, and zoledronic acid was replaced by denosumab. The treatment was then changed to abiraterone acetate and methylprednisolone early in 2012; although a significant reduction of the PSA levels was obtained, this treatment was eventually discontinued because of lack of compliance by the patient. The evolution of PSA and phosphataemia is shown in the [table 1](#).

In 2011, under ketoconazole treatment, the patient's main problem was knee pain. Right knee MRI showed a transversal fracture of the tibia plateau and treatment consisted of total knee prosthesis. The patient's biological results, at that time, were marked hypocalcaemia and hypophosphataemia as shown in [table 1](#). One year later the patient presented walking difficulties; he had difficulty getting up from his chair and was walking by taking small steps. A hip CT scan showed a fracture at the top of the left acetabulum and discrete lytic metastatic lesions of the left sacrum wing. Over the next months the patient developed a severe kyphosis and rib fractures. Treatment with colecalciferol and calcium was started and denosumab was

BACKGROUND

Tumour-associated osteomalacia (TAO) can be caused by a variety of neoplasias; these are usually benign bone or soft tissue tumours. A TAO-like syndrome has also been reported in prostate cancer, small cell lung cancer, haematological malignancies, neurofibromatosis, epidermal nevus syndrome and polyostotic fibrous dysplasia of bone.¹ TAO is a disorder characterised by renal phosphate wasting, hypophosphataemia, inappropriately low serum 1,25-dihydroxyvitamin D levels, normal 25-hydroxyvitamin D level and normal or slightly increased serum parathyroid hormone values.² Fibroblast growth factor 23 (FGF23), phosphatonin, is implicated in the pathogenesis of this syndrome.

Recently, Klotho, a newly discovered antiageing gene, has gained attention in this context. The Klotho gene plays a critical role in regulating ageing and the development of age-related diseases in mammals. The product of that gene, the Klotho protein, can be involved in multiple biological processes.³ It is accepted that, normally, Klotho inhibits insulin and insulin-like growth factor 1 (IGF-1) signalling pathways.^{4 5} In addition, Klotho functions as a coreceptor for FGF23, which downregulates the expression of 1,25-dihydroxyvitamin D3 and phosphate reabsorption.⁶

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discontinued. The patient received a radiotherapy flash on the painful bone metastases without success.

In March 2013 the patient was hospitalised for sudden loss of consciousness that developed at home. At the emergency room he was unconscious and hypothermic (T° 32.9°). His glucose level was 32 mg% and PSA 435.5 ng/mL. Supplemental analysis showed: C peptide 0.33 mg/mL (1.1–4.4), insulin 0.3 mU/L (2.6–24.9), cortisol 8:00 184 mg/mL (62–194) and IGF-1 162 mg/mL (87–541). Oral glucose administration did not control the hypoglycaemia; blood glucose level could be maintained between 80 and 110 mg/dL only with 1 L/24 h intravenous perfusion of 10% glucose.

INVESTIGATIONS

In our patient, a FGF23 value of 454.8 RU/mL (norm 30–176 RU/mL) was obtained in March 2013. This elevated FGF23 was probably due to the prostate tumour, as during this 32 month observation period we had several concomitant PSA and P dosages, allowing us to estimate the correlation between these two blood parameters, with $r = -0.82$ (CI -0.94 to -0.57), $p < 0.0001$, Pearson after PSA log transformation ($n = 17$).

The biological parameters of the patient during the investigated period were presented on table 1. We used the per cent tubular reabsorption of phosphate (%TRP; table 2) to confirm the presence of renal phosphate wasting. The following formula was used to calculate the %TRP

$$\%TRP = 100 \times (1 - ((\text{phosphate/serum phosphate}) \times (\text{serum creatinine/urine creatinine})))$$

When phosphate is normal, the normal range is between 85% and 95%.

OUTCOME AND FOLLOW-UP

The patient died at home in March 2013, 4 years after the diagnosis of prostate cancer, about 2 years after being diagnosed

as refractory to the treatment, strongly invalidating TAO, and a month after the development of tumour-induced hypoglycaemia.

DISCUSSION

The diagnosis of TAO was suspected on the basis of hypophosphataemia resistant to treatment and renal phosphate wasting (table 2). In patients with prostate cancer, since the first report in 1975,⁷ around 25 additional cases of TAO have been described; most of them present with bone metastasis and castration-refractory disease. A single-centre retrospective review in 2005 of 128 patients with hormone-refractory metastatic prostate adenocarcinoma, during a 10-year period from 1989 to 1999, showed that 5.7% of these patients had a serum phosphorus level less than the normal laboratory reference range of 2.5–4.5 mg/dL (0.81–1.45 mmol/L).⁸

FGF23 produced by the tumour is the likely cause for TAO. Fukumoto⁹ showed that FGF23 suppresses phosphate reabsorption by decreasing expression levels of the type 2a and 2c sodium phosphate cotransporter in the brush border membrane of proximal tubules. Physiologically, FGF23 is part of a bone-kidney feedback loop, where circulating 1,25(OH)2D stimulates FGF23 production in bone and FGF23 suppresses 1,25(OH)2D production in the kidney.¹⁰ At the same time, FGF23 decreases the serum phosphate level partly by reducing intestinal phosphate absorption through suppressing the serum 1,25-dihydroxyvitamin D level.

FGF23 acts by binding to target cells via an FGF receptor (FGFR); the signalling requires the coreceptor Klotho.¹¹ Klotho is expressed primarily in the kidney (distal convoluted tubules), parathyroid gland, brain (choroid plexus epithelium) and adipose tissue. The klotho gene, named after one of the Fates of Greek Mythology, the Spinner, was identified in 1997 as a gene mutated in the klotho mouse, which displays an extremely shortened life span with multiple disorders resembling human premature-ageing syndromes.¹² The discovery of the klotho gene has led to the identification of multiple novel endocrine pathways mediated by endocrine FGFs and Klothos, regulating various metabolic processes. The α KL gene product is expressed as multiple species; the membrane-bound form (mKL) associates with FGF23 and FGFRs to signal through the MAPK cascade.^{13 14} Two soluble species of the the Klotho gene proteins have also been reported, an alternatively spliced secreted form (sKL) (exons 1–3 of the 5-exon KL gene) and an endoproteolytic cleavage product of mKL (cKL).⁵

The transmembrane form of Klotho protein (β -Klotho) functions as a coreceptor for FGF23 and regulates phosphate, calcium

Table 1 Biological evolution: PSA, hypophosphataemia and hypocalcaemia

Date	PSA	p Value	Ca	Phase Alc	PTH	Vit D	Crosslaps
08/03/2013	+435.5	<0.3	–5.5	+618		39.0	
24/01/2013	+364.6	–0.8	–7.1	+1009	+272	49.9	0.23
11/09/2012	+143.7	–0.6	7.7	+965	+134	–7.1	+0.95
05/04/2012	+42.67	–0.8	8.0	+1226			
21/02/2012	+179.6	–0.8	8.4	+735			
10/11/2011	+133.1	–1.0	8.5	+1183			
29/06/2011	+56.52	–1.1	8.6	+41			
01/03/2011	+22.49	–0.8	–7.9	+702			
06/01/2011	+28.20	–1.1	8.4	+643			
21/06/2010	+11.32	3.1	9.1	+352			

– Means that the value is under the normal; + means that the value is over the normal.

PSA, prostate specific antigen; normal value: 0.01–2.5 ng/mL.

P, phosphate; normal value: 2.4–4.1 mg/dL.

Ca, calcium; normal value: 8.3–10.2 mg/dL.

Phase Alc, serum alkaline phosphatases; normal value: 10–325 U/L.

PTH, parathyroid hormone; normal value: 15–65 pg/mL.

Vit D, 25(OH) vitamin D; normal value: 30–60 ng/mL.

Crosslaps, degradation products of C-terminal telopeptides of type-I collagen in human serum; normal value: <0.85 ng/mL.

Table 2 Calculated %TRP* in the presented case report—decreased urinary reabsorption

Date	PO4 serum μ mol/L	PO4 urine μ mol/L	Creatine serum μ mol/L	Creatine urine μ mol/L	TPR%
07/03/2013	2.48	67.23	0.007	0.50	–62%
05/12/2012	1.86	84.14	0.011	0.96	–52%
17/10/2012	2.79	60.05	0.10	0.61	–65%
11/09/2012	1.86	47.20	0.012	0.64	–52%
14/08/2012	1.86	86.25	0.009	0.75	–44%

PO4 serum, serum phosphate.

PO4 urine, urine phosphate.

Calculated % TRP*, calculated per cent tubular reabsorption of phosphate.

and vitamin D metabolisms. Defects in either Klotho or FGF23 gene expression cause not only phosphate retention but also a premature-ageing syndrome in mice, unveiling a potential link between phosphate metabolism and ageing. The extracellular domain of Klotho is clipped by the membrane-anchored proteases ADAM10 and ADAM17 in order to generate the secreted form¹⁵ into the blood stream, potentially functioning as an endocrine factor.¹⁶ Secreted and also membrane-bound forms of Klotho can be detected in humans and other mammals. The Klotho extracellular domain does not directly bind to FGF23, but enhances FGF23 binding to its receptor complex with much higher affinity than to FGFR alone, implicating Klotho as a cofactor in FGF23–FGFR interaction and subsequent signalling.¹⁷

In Klotho null mice, FGF23 concentrations are markedly elevated.¹⁸ While serum soluble α -Klotho concentrations are inversely correlated with serum FGF23,¹⁹ direct regulation of α -Klotho by FGF23 has been demonstrated by Dai *et al.*²⁰ Whether FGF23 increases soluble Klotho in blood and whether FGF23 directly or indirectly suppresses Klotho messenger RNA (mRNA) expression is unclear.²¹

By excluding other possible causes of hypoglycaemia in our patient and because of the relative resistance to the substitution treatment, we suspected that the hypoglycaemia observed here was tumour associated. We also hypothesised that the hypoglycaemia was related with the TAO.

Kurosu, *et al.*¹⁴ compared glucose metabolism in Klotho-overexpressing transgenic mice with that in wild-type animals. These studies demonstrate that Klotho overexpression induces resistance to insulin and IGF-1. Klotho-deficient mice are hypoglycaemic and extremely sensitive to insulin.^{5 22} These observations suggest that Klotho may inhibit the insulin/IGF-1 signalling pathway. In fact, secreted Klotho protein has an activity that inhibits insulin-induced and IGF-1-induced autophosphorylation of insulin receptor and IGF-1 receptor when applied to cultured cells.²³ Although the mechanism for this activity remains to be determined, it is possible that secreted Klotho protein may modify glycans of the insulin/IGF-1 receptors, which inhibits their activity and/or alters cell surface abundance.

There are some data in favour of our hypothesis, as β -Klotho is involved in FGF-21 signalling.²⁴ The FGF-21 can regulate insulin-independent glucose transport in adipocytes.²⁵ Systemic administration of FGF-21 to diabetic animals led to a significant reduction in blood glucose and triglyceride levels, and Fgf21-transgenic mice, which overexpress FGF-21, were resistant to obesity induced by a high-fat diet.²⁶ The recombinant FGF-21 protein retains its biological activity in Klb^{−/−} mice, suggesting the existence of a β -Klotho-independent signalling pathway involving FGF-21.²⁷ Genetically abolishing Klotho function in mice by knockout or knockdown of Kl resulted in the generation of lean mice with decreased white adipose tissue accumulation, including a reduced subcutaneous adipose tissue layer compared with that in wild-type mice.²⁸ Intracellular lipid accumulation, particularly in skeletal muscle and liver, is usually associated with insulin resistance. Importantly, reducing obesity via the genetic elimination of Klotho in Lepob/ob mice subsequently crossed with Kl^{−/−} mice also reduced blood glucose levels in the resulting Kl^{−/−}Lepob/ob mice, suggesting that Klotho might influence glucose metabolism as well as adipogenesis.²⁸ The *in vivo* manipulation of Klotho function affects glucose metabolism; Klkl/kl mice have reduced pancreatic insulin content but still develop hypoglycaemia owing to increased insulin sensitivity. After insulin injections, blood glucose levels were markedly reduced in Klkl/kl mice relative to those in

wild-type controls.^{28 29} Hepatic glucose synthesis also has a key role in maintaining systemic glucose metabolism. Analyses of glucose tolerance and insulin tolerance show that, compared with Lepob/ob mice, double-mutant Kl^{−/−}Lepob/ob mice have greater insulin sensitivity and better glucose tolerance, which clearly suggests that Klotho has a role in the hyperglycaemia observed in Lepob/ob mice.²⁸ Whether reducing Klotho activity in humans would have beneficial effects similar to those observed in Kl^{−/−}Lepob/ob mice is unclear and warrants further study.

In an Occam's Razor perspective, we hypothesised that the two paraneoplastic manifestations in our patient (TAO and refractory hypoglycaemia) were due to one cause chain with two main nodes. The Occam's Razor pushes the selection of a preferred hypothesis, based on the clinical presentation. In our case report it is the FGF23 hyperproduction responsible for the TAO, which was confirmed by a level of 454.8 RU/mL (30–176) in the serum (March 2013). As shown, this hypothesis is compatible with the literature reports and thus has a physiopathological basis. Second, since a downregulation of α -Klotho/FGF23 coreceptor expression has been described as a result of high-circulating FGF23,²⁰ we speculated a direct role of Klotho in insulin sensitivity, as has been shown in animal models.²⁴

Learning points

- Tumour-associated osteomalacia (TAO) is a paraneoplastic syndrome characterised by osteomalacia secondary to renal phosphate wasting, leading to severe hypophosphataemia.
- Patients with TAO often present with many years of symptoms before they are diagnosed. Common symptoms such as in the case of our patient are bone pain, muscle weakness and multiple fractures.
- When TAO is suspected and hypophosphataemia is present, the presence of renal phosphate wasting should be confirmed. The dosing of fibroblast growth factor 23 (FGF23) should be considered.
- FGF23 is the likely cause of TAO and α -Klotho functions as a coreceptor, which can be responsible for tumour-associated symptoms such as hypoglycaemia.

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