

Brief Report

OCTREOTIDE THERAPY FOR
TUMOR-INDUCED OSTEOMALACIA

JOCHEN SEUFERT, M.D., KATJA EBERT, M.D.,
JUSTUS MÜLLER, M.D., JOCHEN EULERT, M.D.,
CHRISTIAN HENDRICH, M.D., EDGAR WERNER, M.D.,
NORBERT SCHÜTZE, PH.D., GEORG SCHULZ, M.D.,
WERNER KENN, M.D., HUBERT RICHTMANN, M.D.,
KLAUS-DIETER PALITZSCH, M.D., AND FRANZ JAKOB, M.D.

TUMOR-induced osteomalacia (also known as oncogenic osteomalacia)¹ is a rare disorder characterized by phosphaturia, hypophosphatemia, and osteomalacia mimicking the clinical phenotype of either X-linked² or autosomal dominant³ hereditary hypophosphatemic rickets. Tumor-induced osteomalacia develops because of tumors that are predominantly of benign mesenchymal origin⁴ but that may occasionally be malignant, as was recently reported.⁵ Surgical removal of the tumor relieves all symptoms. Hemangiopericytoma is the most dominant histologic entity in tumor-induced osteomalacia.^{4,6} Paraneoplastic secretion by the tumor of an unknown factor or factors — termed “phosphatonin” — causing renal tubular phosphate wasting has been proposed as the pathogenic mechanism.⁷

We describe an adult man who had hypophosphatemic osteomalacia for several years before an octreotide scan revealed a mesenchymal tumor in his left thigh. Moreover, subcutaneous administration of octreotide, a synthetic somatostatin analogue, abolished renal tubular phosphate wasting before subsequent surgical removal of the tumor.

CASE REPORT

A 50-year-old man presented with chronic pain of the spine, ribs, femurs, and tibias. The clinical examination was otherwise normal. There was no family history of metabolic bone disease.

The initial evaluation in July 1997 revealed elevated urinary phosphorus excretion, low serum phosphorus levels, and elevated serum alkaline phosphatase and osteocalcin levels. The serum values for calcium, parathyroid hormone, 25-hydroxyvitamin D₃, and calcitonin were normal; the serum value for 1,25-dihydroxy-

vitamin D₃ was inappropriately low (6.9 pg per milliliter; normal range, 35 to 80). The diagnostic evaluation at this time provided no evidence of tumor. Multiple rib fractures were identified. A bone scan with technetium-99m-labeled 2,3-dicarboxypropane-1,1-diphosphonate showed a pattern of focal, late-phase enhancement in the spine and ribs; this was suggestive of metabolic bone disease. The patient was given the diagnosis of idiopathic hypophosphatemic osteomalacia with renal phosphate wasting. Continuous oral supplementation with phosphate and 1,25-dihydroxyvitamin D₃ (1.25 μg per day) was initiated. Three years after the initial diagnosis, progressive metabolic bone disease prompted another extensive evaluation.

METHODS

Assays

Serum, plasma, and urinary constituents were measured by standard techniques. Hormone measurements were performed with the use of commercial immunoassay kits. Assays of serum parathyroid hormone, 25-hydroxyvitamin D₃, 1,25-dihydroxyvitamin D₃, and calcitonin were performed with commercial kits (DPC Biermann, Bad Nauheim, Germany), as were those for osteocalcin (Diagnostic Systems Laboratories, Sinsheim, Germany) and urinary type I collagen C-telopeptides (Beckmann Coulter, Krefeld, Germany). For calculation of renal clearance of phosphate, serum and urinary concentrations of phosphorus were determined together with the excreted urinary volume during two one-hour collection periods (Table 1).

Values for the threshold for renal tubular reabsorption of phosphate were derived from the nomogram provided by Walton and Bijvoet.⁸ The excreted urinary volume was quantified during a two-hour collection period in the morning, and urinary phosphate and creatinine levels were determined.

Imaging Studies and Octreotide Therapy

We performed nuclear magnetic resonance, angiographic, and scintigraphic studies using octreotide labeled with indium-111 as a tracer according to standard techniques. Before surgery, unlabeled octreotide (Sandostatin, Novartis Pharma, Nuremberg, Germany) was administered subcutaneously at a dose of 50 μg three times a day for five days and then at a dose of 100 μg three times a day for eight days.

Expression of Somatostatin-Receptor Subtypes

Expression of messenger RNA (mRNA) for somatostatin-receptor subtypes in tumor samples was analyzed by the reverse-transcriptase-polymerase chain reaction (RT-PCR). Total RNA was extracted from tumor tissue by a modified single-step technique (Trizol, GIBCO, Life Technologies, Gaithersburg, Md.). RNA was reverse transcribed with use of oligo-dT₁₂₋₁₈ primers with reverse transcriptase (Superscript, GIBCO, Life Technologies). For PCR reactions, the following oligonucleotides specific for human somatostatin receptor subtypes 1, 2, 3, 4, and 5 were used: somatostatin receptor subtype 1 (318-bp PCR product), sense primer, 5'ATGGTGGCCCTCAAGGCCGG3', antisense primer, 5'CGCGGTGGCGTAATAGTCAA3'; somatostatin receptor subtype 2 (318-bp PCR product), sense primer, 5'TCCTCTGGAATCCGAGTGGG3', antisense primer, 5'TTGTCCTGCTTACTGTCCT3'; somatostatin receptor subtype 3 (332-bp PCR product), sense primer, 5'TGCCACCCTGGGCAACGTGT3', antisense primer, 5'CAGGCAGAATATGCTGGTGA3'; somatostatin receptor subtype 4 (323-bp PCR product), sense primer, 5'GCGCGCGGCGACCTACCGGC3', antisense primer, 5'GCCTGGTGATTTCTTCTCC3'; and somatostatin receptor subtype 5 (259-bp PCR product), sense primer, 5'CTGGTGGGCGCGCCGCTC3', antisense primer, 5'CCAGGCGGCACAGGACGGGG3'. The cycling conditions for the PCR reactions were 1 cycle at 94°C for 2 minutes and 28 cycles at 94°C for 30 seconds, 62°C for 30 seconds, and 72°C for 45 seconds. The identity of the PCR products was confirmed by sequencing (data not shown).

From the Division of Endocrinology, Metabolism, and Molecular Medicine, Medizinische Poliklinik (J.S., K.E., F.J.); and the Departments of Pathology (J.M.), Orthopedic Surgery (J.E., C.H., N.S.), Nuclear Medicine (E.W.), and Radiology (G.S., W.K.), University of Würzburg — both in Würzburg; the Division of Endocrinology of the Department of Internal Medicine I, University of Regensburg, Regensburg (K.-D.P.); and Tirschenreuth (H.R.) — all in Germany. Address reprint requests to Dr. Jakob at the Division of Endocrinology, Metabolism, and Molecular Medicine, Medizinische Poliklinik, University of Würzburg, Klinikstr. 6-8, 97070 Würzburg, Germany, or at jakob.medpoli@mail.uni-wuerzburg.de.

TABLE 1. LABORATORY FINDINGS IN A PATIENT WITH RENAL TUBULAR PHOSPHATE WASTING AND VITAMIN D-RESISTANT OSTEOMALACIA BEFORE AND 10 DAYS AFTER OCTREOTIDE THERAPY AND 18 MONTHS AFTER SURGICAL REMOVAL OF THE TUMOR.*

VARIABLE	NORMAL RANGE	VALUE BEFORE OCTREOTIDE THERAPY	VALUE AFTER OCTREOTIDE THERAPY	VALUE AFTER TUMOR REMOVAL
Serum				
Alkaline phosphatase (U/liter)	55–170	326	241	143
Phosphorus (mmol/liter)	0.87–1.45	0.61	1.41	1.36
Calcium (mmol/liter)	2.0–2.7	2.2	2.3	2.5
Sodium (mmol/liter)	135–145	139	141	139
Potassium (mmol/liter)	3.5–5.0	4.3	4.1	3.9
Chloride (mmol/liter)	94–110	100	103	104
Magnesium (mmol/liter)	0.70–1.05	0.77	0.83	0.79
Creatinine (mg/dl)	0.8–1.3	0.9	0.9	1.0
Blood urea nitrogen (mg/dl)	4.7–23.0	21.9	20.7	15.4
Parathyroid hormone (pg/ml)	12.0–72.0	37.6	109.3	22.8
Parathyroid hormone-related protein (pmol/liter)	0–2.5	0.2	0.3	0.2
25-Hydroxyvitamin D ₃ (ng/ml)	6.5–54.8	23.3	13.2	27.6
1,25-Dihydroxyvitamin D ₃ (pg/ml)	35.0–80.0	47.0	52.6	49.0
Calcitonin (pmol/liter)	0–3.2	0.6	0.9	1.4
Osteocalcin (μg/liter)	3.0–8.0	41.0	8.1	3.7
Growth hormone (ng/ml)	0–5.0	1.1	1.9	1.7
Insulin-like growth factor I (ng/ml)	83–291	129	121	119
Urine				
Phosphorus (mmol/day)	10.0–32.0	62.9	13.7	21.7
Calcium (mmol/day)	3.0–6.0	0.5	2.9	3.5
Sodium (mmol/day)	130–280	280	268	265
Potassium (mmol/day)	51.0–100.0	59.6	52.4	57.3
Chloride (mmol/day)	80–270	224	205	201
Creatinine clearance (ml/min)	98.0–156.0	103.9	107.5	127.7
Type I collagen C-telopeptides (mg/mol)	170–410	564	1141	262
Phosphate clearance (ml/min)†	5.4–16.2	69.6	15.9	11.1
Threshold for renal tubular reabsorption of phosphate (mmol/liter)‡	0.8–1.4	0.6	1.2	1.4

*To convert values for creatinine to micromoles per liter, multiply by 88.4. To convert values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert values for parathyroid hormone to picomoles per liter, multiply by 0.106. To convert values for 25-hydroxyvitamin D₃ to nanomoles per liter, multiply by 2.496. To convert values for 1,25-dihydroxyvitamin D₃ to picomoles per liter, multiply by 2.4. To convert values for calcitonin to picomoles per liter, multiply by 0.2926. To convert values for growth hormone to picomoles per liter, multiply by 0.0465. To convert values for insulin-like growth factor I to nanomoles per liter, multiply by 0.131. Serum levels of 1,25-dihydroxyvitamin D₃ before and after octreotide therapy were measured while the patient was receiving oral supplementation with 1,25-dihydroxyvitamin D₃ (1.25 μg per day).

†Renal phosphate clearance was calculated according to the following formula:

$$C_p \text{ (ml/min)} = \frac{P_u \text{ (mg/dl)} \times \text{Vol}_u \text{ (ml)}}{P_s \text{ (mg/dl)} \times \text{Time (min)}}$$

where C_p denotes renal phosphate clearance, P_u urinary phosphorus concentration, Vol_u excreted urinary volume during the collection period, P_s serum phosphorus concentration, and Time the duration of the collection period.

‡Renal tubular reabsorption of phosphate was calculated according to the following formula:

$$\text{TRP} = 1 - \left(\frac{C_p}{C_{cr}} \right)$$

where TRP denotes renal tubular reabsorption of phosphate, C_p renal phosphate clearance, and C_{cr} creatinine clearance. With the use of values for TRP and serum phosphorus, the threshold for TRP was derived from the nomogram of Walton and Bijvoet.⁸

Expression of mRNA for Matrix Extracellular Phosphoglycoprotein and Fibroblast Growth Factor 23

Expression of mRNA for matrix extracellular phosphoglycoprotein and fibroblast growth factor 23 in tumor samples was analyzed by RT-PCR. The PCR conditions for matrix extracellular phosphoglycoprotein were as previously described.⁹

The following oligonucleotides were used for fibroblast growth factor 23: sense primer, 5'GGCGCACCCCATCAGACCATC3', and antisense primer, 5'GCCCGTTCCCCAGCGTGCCTGTT3'. The cycling conditions for the PCR reactions were 1 cycle at 94°C for 2 minutes and 28 cycles at 94°C for 30 seconds, 60°C for 30 seconds, and 72°C for 45 seconds. The identity of the PCR products was confirmed by sequencing (data not shown).

RESULTS

Excessive osteomalacia with osteoidosis (an excess of nonmineralized organic bone matrix) was found in a bone-biopsy specimen derived from the iliac crest. Laboratory findings are summarized in Table 1. Findings consistent with the diagnosis of renal phosphate wasting included elevated renal phosphate clearance and low serum phosphorus levels despite ongoing oral phosphate therapy. The serum level of 1,25-dihydroxyvitamin D₃ was at the lower end of the normal range despite oral supplementation. The threshold for renal tubular reabsorption of phosphate, which is largely independent of oral phosphate therapy, was significantly reduced. The serum levels of alkaline phosphatase, osteocalcin, and urinary type I collagen C-telopeptides were elevated.

Since we were unable to locate a tumor, an octreotide scan was performed that showed circumscribed pooling of radioactive octreotide tracer in the left thigh (Fig. 1A). Magnetic resonance imaging and angiography revealed a well-vascularized mass of 5.5 by 4.5 by 3.0 cm within the laterodorsal section of the vastus lateralis muscle (Fig. 1B).

While the patient awaited surgical resection of the tumor, a trial of subcutaneous octreotide was initi-

ated and continued for 13 days (50 μ g three times a day on days 1 through 5 and 100 μ g three times a day on days 6 through 13). Octreotide therapy led to normalization of serum phosphorus levels, phosphate clearance, and the threshold for renal tubular reabsorption of phosphate by day 10 (Table 1 and Fig. 2). Serum alkaline phosphatase and osteocalcin levels were reduced, whereas urinary excretion of type I collagen C-telopeptide and serum parathyroid hormone levels were transiently increased. Serum calcium levels as well as all other values remained unchanged (Table 1).

Oral phosphate therapy was tapered as serum phosphorus levels became normal (Table 1 and Fig. 2). The tumor was a hemangiopericytoma with slit-like vessels, pericytic tumor cells with elongated nuclei, crowding of the nuclear membrane, and dense chromatin surrounded by a small, elongated cytoplasmic region. Tumor cells stained positive for vimentin but were negative for smooth-muscle α -actin, desmin, keratin markers, CD34, CD31, S100 protein, and HMB-45. The proportion of cells with a proliferative phenotype was less than 10 percent. Mitotic figures, necrotic areas of the tumor, invasion of blood vessels, and cytologic atypia could not be found (data not shown).

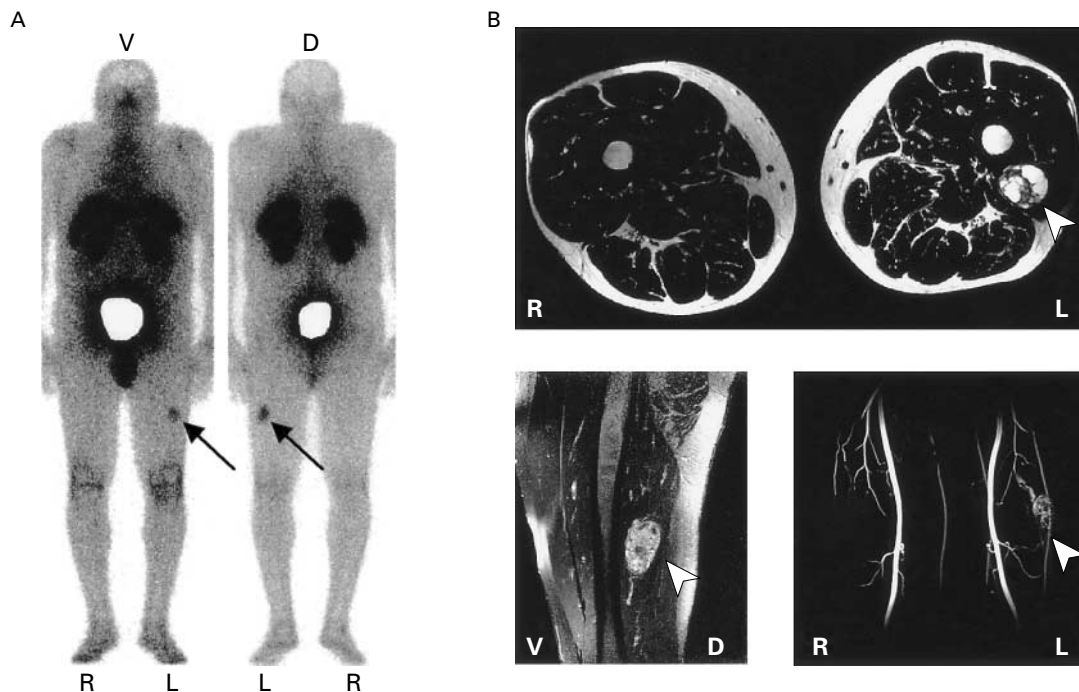


Figure 1. Imaging Studies in a Patient with Tumor-Induced Osteomalacia.

Panel A shows scintigraphic images obtained four hours after injection of 230 MBq of octreotide labeled with indium-111. Circumscriptive pooling of radiolabeled octreotide is demonstrated within the lateral portion of the left thigh (arrows). In Panel B, nuclear magnetic resonance imaging in transverse sections (top) and longitudinal sections (bottom left) reveals a tumor with heterogeneous contrast enhancement within the laterodorsal portion of the vastus lateralis muscle in the left thigh (arrowheads). Magnetic resonance angiography (bottom right) shows highly perfused arterial and venous vessels in the tumor (arrowhead). R denotes right, L left, V ventral, and D dorsal.

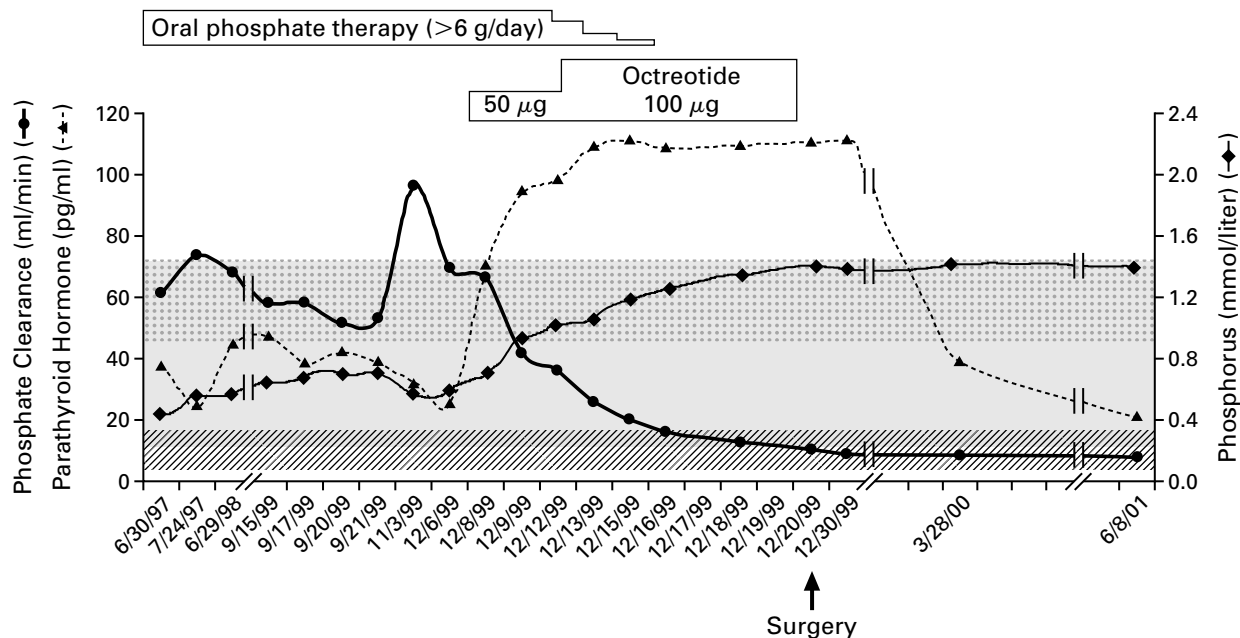


Figure 2. Renal Phosphate Clearance and Values for Serum Phosphorus and Parathyroid Hormone in a Patient with Tumor-Induced Osteomalacia during the Initial Course of the Disease, during Octreotide Therapy before Surgical Removal of the Tumor, and after Surgical Removal of the Tumor.

The normal range of values for renal phosphate clearance (5.4 to 16.2 ml per minute) is indicated by the hatched area. The normal range of values for serum parathyroid hormone (12 to 72 pg per milliliter) is indicated by the shaded area. The normal range of values for serum phosphorus (0.87 to 1.45 mmol per liter) is indicated by the stippled area. To convert values for serum parathyroid hormone to picomoles per liter, multiply by 0.106. Doses of octreotide were administered subcutaneously three times a day.

Since removal of the tumor, phosphate metabolism has remained normal without further oral phosphate therapy (Fig. 2).

RT-PCR analysis of tumor-derived RNA samples showed predominant expression of somatostatin receptor subtype 2 mRNA and a faint positive reaction for somatostatin receptor subtype 5 mRNA, whereas subtypes 1, 3, and 4 were absent (Fig. 3). The mRNA for matrix extracellular phosphoglycoprotein⁸ and fibroblast growth factor 23 was abundantly expressed (Fig. 4).

Clinical and laboratory evaluations 3 and 18 months after surgery revealed normalization of bone and phosphate metabolism (Table 1 and Fig. 2). Another bone biopsy as well as follow-up scintigraphic imaging 18 months after surgery demonstrated resolution of all signs of metabolic bone disease and osteomalacia (data not shown).

DISCUSSION

Tumor-induced osteomalacia with tumors that are predominantly derived from the mesenchyme is a paraneoplastic syndrome of renal phosphate wasting due to secretion of phosphaturic factors, termed phos-

phatonins.¹ Because the tumor caused no symptoms in our patient, diagnosis of the tumor was delayed for several years. We hypothesized that tumors secreting phosphatonins may express somatostatin receptors that regulate secretory activity, as has been shown in other endocrine tumors.^{10,11} We were able to detect a previously unrecognized tumor by scintigraphy using octreotide labeled with indium-111, as has been done in similar cases.^{10,11} In addition, we were able to achieve complete preoperative remission of renal phosphate wasting in our patient by octreotide therapy through a mechanism that most likely involved suppression of phosphatonin secretion.

The finding of somatostatin receptor subtype 2 expression in the tumor provides the molecular basis for the positive octreotide scan and the clinical response to octreotide therapy (Table 1 and Fig. 2), because subtype 2 displays the highest affinity for octreotide of all five somatostatin-receptor isoforms.¹²

Phosphate metabolism in humans is regulated by hormonally modified intestinal uptake and renal excretion, through interaction with the vitamin D–parathyroid hormone–calcium endocrine system.¹³ 1,25-Dihydroxyvitamin D₃ stimulates intestinal uptake of

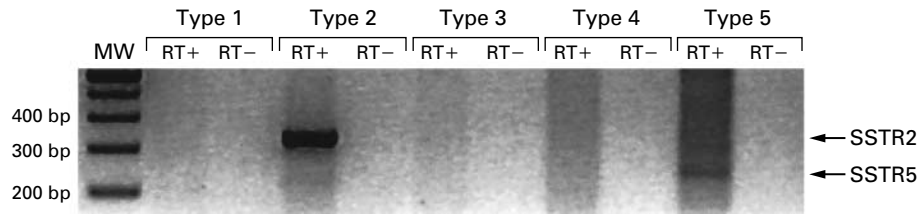


Figure 3. Expression of mRNA for Somatostatin Receptor Subtypes 1, 2, 3, 4, and 5 in a Tumor from a Patient with Tumor-Induced Osteomalacia.

The results of RT-PCR with oligonucleotides specific for somatostatin receptor subtypes 1, 2, 3, 4, and 5 are shown. RT- denotes PCR products derived from a reverse transcription without addition of reverse transcriptase (as a control for genomic-DNA contamination in RNA extracted from the tumor). The tumor predominantly expressed mRNA for somatostatin receptor subtype 2 and (less abundantly) type 5. MW denotes the molecular-weight marker, and SSTR somatostatin-receptor subtype.

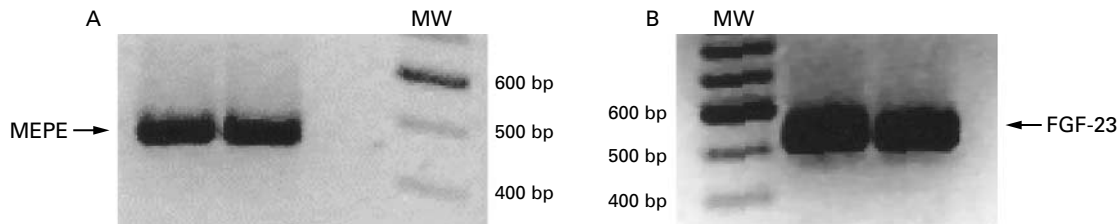


Figure 4. The mRNA Expression of Secreted Tumor Factors.

Panel A shows detection of mRNA expression for the tumor factor matrix extracellular phosphoglycoprotein (MEPE) by RT-PCR in two independent tumor samples. Panel B shows detection of mRNA expression for the phosphaturic factor fibroblast growth factor 23 (FGF-23) by RT-PCR in two independent tumor samples. The tumor expressed mRNA for both matrix extracellular phosphoglycoprotein and fibroblast growth factor 23. MW denotes the molecular-weight marker.

phosphate and inhibits renal excretion,¹⁴ whereas parathyroid hormone is phosphaturic.¹⁵ Renal phosphate excretion is regulated mainly through the activity of the renal tubular type IIa sodium–inorganic phosphate cotransporter.¹⁶ Studies of hereditary and tumor-associated phosphate-wasting disorders suggest that several other factors must be involved in the regulation of phosphate metabolism. The present view holds that the product of the *PHEX* gene (phosphate-regulating gene with homologies to endopeptidases on the X chromosome) is an endopeptidase that cleaves secreted phosphaturic hormone–like substances — the phosphatonins.^{1,17} Thus, hypophosphatemic rickets may be caused by disorders of the sodium–inorganic phosphate cotransporter itself, of the phosphatonins as modifiers of renal phosphate transport, or of the endopeptidase PHEX, which cleaves phosphatonins. In support of this concept, inactivating mutations of the *PHEX* gene are associated with the clinical phenotype of X-linked hypophosphatemic rickets.²

The tumor-induced form of hypophosphatemic rickets (oncogenic osteomalacia) has recently been shown to be associated with overexpression of fibroblast growth factor type 23 in tumor cells, which indicates that fibroblast growth factor type 23 is one of the causative phosphatonins for this disease.¹⁸ We found ample expression of the phosphatonin fibroblast growth factor type 23 in our patient's tumor. Thus, the clinical response to octreotide therapy in this patient may suggest that secretion of fibroblast growth factor type 23 by the tumor can be modulated through the somatostatin-receptor signaling pathway. This protein has further been demonstrated to act as both a substrate for the endopeptidase PHEX and an inhibitor of phosphate transport in kidney cells.¹⁹ Moreover, in the autosomal dominant form of hypophosphatemic rickets, mutations in fibroblast growth factor type 23 have been identified that render the molecule resistant to cleavage by PHEX.³

The patient's laboratory values provided no evidence of major effects of octreotide therapy on glo-

merular filtration or renal perfusion through the growth hormone–insulin-like growth factor I axis (Table 1). In patients with acromegaly who were treated with octreotide, minor increases in serum parathyroid hormone levels within the normal range have previously been reported.²⁰ We believe, however, that the main reason for the transient overt hyperparathyroidism in our patient was the normalization of serum phosphorus levels that led to a disinhibition of secretion of parathyroid hormone (Table 1 and Fig. 2), despite unchanged serum calcium levels.

We conclude that octreotide imaging is a valuable diagnostic tool in patients with phosphate wasting but with no family history and with no clinically apparent tumor. Moreover, we propose that in patients in whom surgery cannot be performed for technical reasons or because of coexisting conditions, phosphate wasting may be relieved by treatment with somatostatin analogues, given that the tumor expresses somatostatin receptors, which can easily be evaluated by octreotide scanning.

This case suggests that regulation of phosphate metabolism involves secretory mechanisms that may be modulated by somatostatin receptors. Whether this holds true only under pathologic conditions or is relevant to phosphate metabolism in normal states remains to be elucidated.

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