

## A case of oncogenic osteomalacia detected by <sup>111</sup>In-pentetreotide total body scan

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### ABSTRACT

*A case of tumor-induced osteomalacia in a 35-year-old woman suffering from severe bone pain and muscle weakness is described. This uncommon disease is characterized by a reduced serum phosphorus level with elevated urinary phosphate excretion, normocalcemia, high serum bone alkaline phosphatase and a deficiency of 1,25 dihydroxyvitamin D<sub>3</sub>. The tumors responsible for oncogenic osteomalacia are usually small, benign and commonly located in bone or soft tissues of the head and the limbs, so the diagnosis can often be difficult. In this case a <sup>111</sup>In-pentetreotide scintigraphy was able to detect a hemangiopericytoma located in the right maxillary sinus. Removal of the tumor resulted in the reversal of clinical and biochemical abnormalities.*

### Introduction

Tumor-induced osteomalacia (TIO) is a rare and insidious paraneoplastic syndrome characterized by acquired hypophosphatemia, hyperphosphaturia and low serum levels of 1,25 dihydroxyvitamin D<sub>3</sub>. Usually, patients complain of muscle weakness, bone and muscle pain with gradual onset. These symptoms commonly involve weight-bearing areas such as the legs, ankles, hips and back. Following surgical removal of the tumor the clinical and biochemical abnormalities disappear, indicating that they are due to a humoral factor secreted by the tumor (1, 2).

The responsible tumor, often a benign mesenchymal tumor, may be located in almost any part of the body, with a large proportion occurring in the head and in the upper and lower extremities. To date there is no standard method for detecting these tumors. The finding of somatostatin receptors expressed by human mesenchymal tumors (3-5) opens a new pathway for the diagnosis of this disease, as demonstrated in some other cases (6).

Here we report a case of TIO in which the lesion was finally detected by <sup>111</sup>In-pentetreotide scintigraphy and successfully removed.

### Case report

A 35-year-old Caucasian woman was

admitted to our hospital because of severe bone pain, polyarthralgia and muscle weakness. The patient had been healthy until two years before admission, when she began to complain of pain in the ankles and knees on weight bearing but gradually subsiding with rest. These symptoms seriously worsened in the last nine months. Her gait was anserine, the weakness and bone pain became so severe and disabling that the patient was not able to walk unassisted. No response to nonsteroidal antiinflammatory and steroidal medications (prescribed by the general practitioner) was reported. She had lost 9 Kg in weight in the last year and 5 cm in height. There was no family diagnosis of bone or renal disease. The patient did not have a history of risk factors for bone disorders. On physical examination there was no evidence of synovitis, but the motion of the hips was limited. There were no neurological deficits.

Laboratory tests showed extreme hypophosphatemia 0.7 mg/dl (normal range, 2.5-4.6 mg/dl), mild hypocalcemia 7.8 mg/dl (normal range, 8.4-10.2 mg/dl), an increase in total alkaline phosphatase of 194 U/L (normal range, 32-92 U/L) with bone isoenzyme as high as 72% (normal range, < 35%). Urinary phosphate excretion was 458 mg/24h (normal range, 400-1000 mg/24h), the renal clearance of phosphate was 26.3 ml/min (normal range, 6-15 ml/min). Urinary calcium excretion was 59 mg/24h (normal range, 100-300 mg/24h). The level of 1.25(OH)<sub>2</sub>D<sub>3</sub> was low (7 pg/ml; normal range, 14-50 pg/ml) with normal plasma concentrations of 25OHD<sub>3</sub>. Other laboratory investigations, including parathyroid hormone, protein electrophoresis, creatinine, liver and thyroid function tests, muscle enzymes, erythrocyte sedimentation rate, blood cell count were in the normal range.

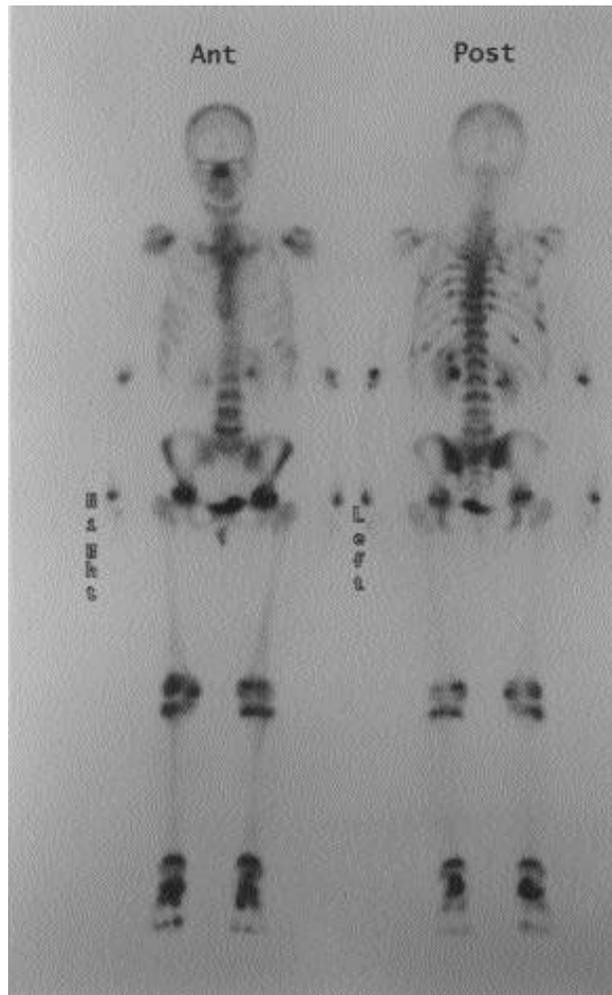
On plain radiographs many thoracic and lumbar vertebrae showed bowing of the endplates without abnormalities in the remainder of the skeleton, except for a diffuse loss of radiodensity. Bone densitometry (DXA; Hologic 4500) revealed decreased bone mass in the spine and normal values in the femoral neck. The value of the lumbar measure-

ment (L2-L4) was  $0.779\text{g}/\text{cm}^2$  corresponding to  $-2.72$  T score.

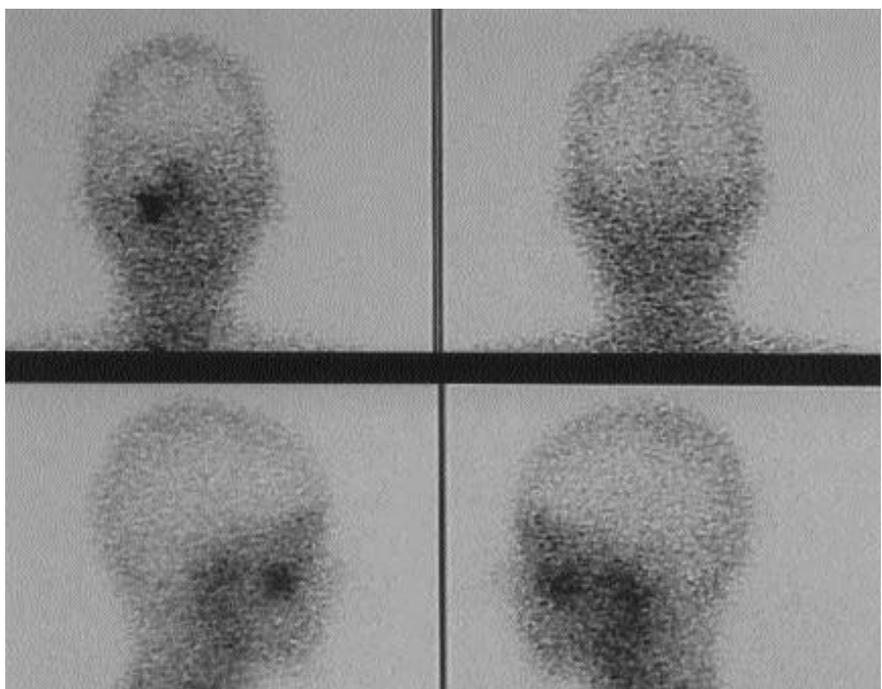
A bone scintigraphy was performed: the acquisition was done 3 hours after the injection of  $555\text{ MBq}$  ( $15\text{ mCi}$ ) of  $^{99\text{m}}\text{Tc}$  metilen-diphosfonate, whole body technique, with a double head gamma camera PRISM 2000 XP (Picker) matrix acquisition  $1024 \times 256$  pixel ( $2000\text{ KC}$  count). Diffuse increased uptake corresponding to the meta-epiphysal region of both femuri, tibiae, radii and humeri was discovered. An enhanced radiotracer uptake was also shown by six ribs and four vertebrae, probably due to recent fractures (Fig. 1).

The clinical, laboratory and radiological features were consistent with the diagnosis of hypophosphatemic osteomalacia. A bone biopsy of the iliac crest showed a thickened layer of unmineralized osteoid consistent with osteomalacia. Further investigations excluded primary renal and bowel diseases.

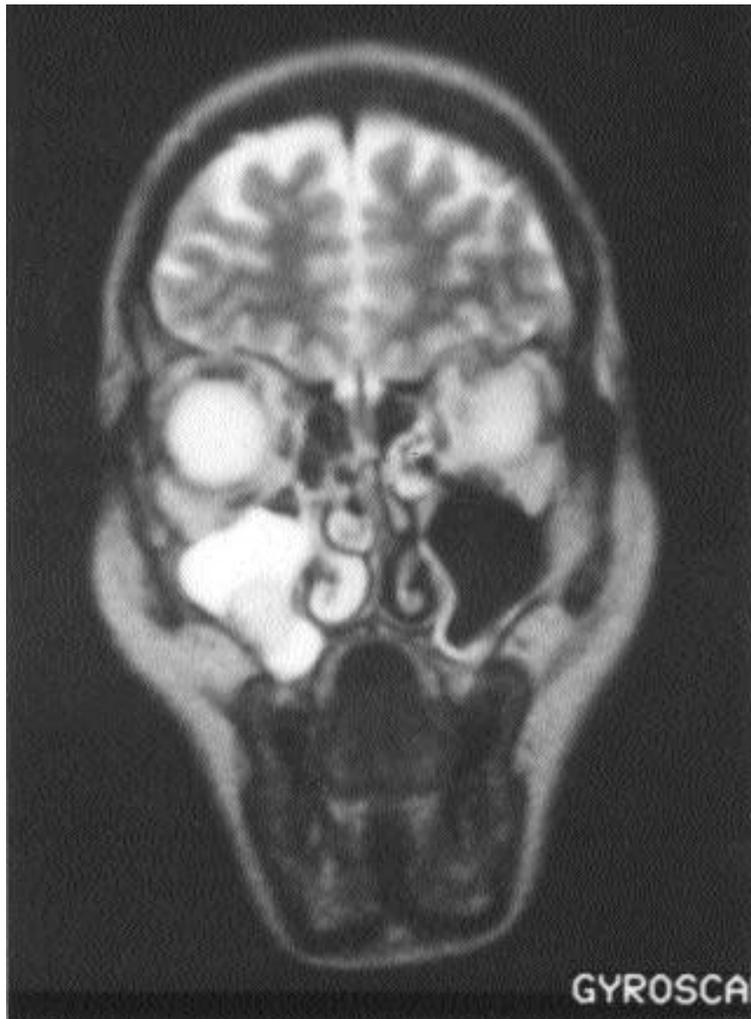
In the search of an underlying tumor a total body scan was performed with pentetotide 4 and 24 hours after injection of  $111\text{ MBq}$  ( $3\text{ mCi}$ ) of  $^{111}\text{In}$ -octreoscan (Byk Gulden-Italia). Two large field of view digital SPET cameras (General Electric-Millennium VG) with medium energy, general purpose collimator and two energy peaks of  $171$  and  $245\text{ keV}$  ( $20\%$  window) were used. Total body images in anterior and posterior views (scan speed  $12\text{ cm} \times \text{min}^{-1}$ , matrix acquisition  $128 \times 512$ ) were supplemented with appropriate planar views. Abnormal  $^{111}\text{In}$ -octreoscan tumor uptake was defined as any focal or diffuse area of increased activity in a location incompatible with normal anatomy. In this case an increased uptake in the right maxillary sinus was disclosed (Fig. 2). Magnetic resonance imaging (MRI) confirmed the presence of a solid round mass,  $2\text{ cm}$  in diameter, in the right maxillary sinus. There was no destruction of the bone wall (Fig. 3). While waiting for surgery, the patient received daily supplementation with phosphate  $2\text{ g}$ , calcium carbonate  $2\text{ g}$ ,  $1.25(\text{OH})_2\text{D}_3$   $1.5\text{ mcg}$ . The serum phosphate level increased up to a maximum value of  $2.3\text{ mg}/\text{dl}$ . The urinary phosphate excretion increased as well



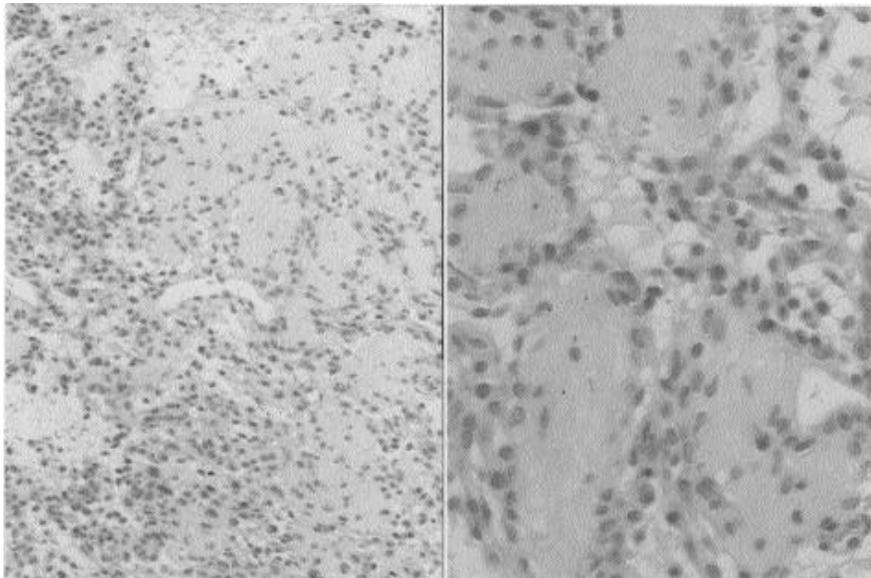
**Fig. 1.** Bone scintigraphy showing increased uptake corresponding to the meta-epiphysal region of both femuri, tibiae, radii, humeri, six ribs and four vertebrae.



**Fig. 2.**  $^{111}\text{In}$ -pentetreotide scintigraphy. A spot of increased radiotracer uptake can be observed in correspondence to the right maxillary sinus revealing the tumor.



**Fig. 3.** Coronal SE T2-weighted MR image of the skull reveals opacification of the right maxillary sinus. A round soft tissue mass, 2 cm in diameter, can be seen along the inferior aspect of the sinus. The mass shows homogeneous, intermediate signal intensity. No destruction of the bone wall is detected.



**Fig. 4.** The histology of the tumor: pattern hemangiopericytoma-like (x10, x25) (see text).

and reached a maximum value of 2145 mg/24h.

Removal of the tumor resolved the biochemical abnormalities in a few days. Two weeks after surgery and withdrawal of oral therapy, her serum phosphate level increased up to 4 mg/dl and there was a rapid decrease in urinary phosphate excretion to 609 mg/24h. The value of  $1.25(\text{OH})_2\text{D}_3$  returned to the normal range. As shown in Figure 4, histologically the tumor was composed of epithelioid cells, range from round or oval to slightly spindle and are arranged in a various patterns including nests and cords, with elaborated and ramifying blood vessels (pattern hemangiopericytoma-like). Cytological atypis was minimal and mitoses were rare. The cells are separated by osteoid matrix and focally by hyalinized collagen.

Bone densitometry performed 8 months after surgery showed a value for the lumbar scan of  $0.950 \text{ g/cm}^2$  corresponding to a percentual increase of 21.9%.

The patient showed progressive improvement in her symptoms with a complete recovery in three months.

#### Discussion

After the description of an acquired osteomalacia resistant to vitamin D supplementation by McCance in 1947 (7), Prader *et al.* in 1959 first described a case of oncogenic osteomalacia in which a tumour was recognised as the cause of osteomalacia (8), and to date about 120 cases of TIO have been reported in the literature. The majority of patients are adults over 30 years (range 1-74), with a male:female ratio of 1.2: 1. The duration of symptoms before diagnosis ranges from 2.5 months to 19 years, with an average of more than 2.5 years (1). The musculoskeletal symptoms of TIO (gradual onset of muscular weakness and bone pain on weight-bearing areas such as legs, ankles hips and back; fatigue and gait disturbances) are non-specific and unrevealing. The radiological features of osteopenia and pseudofractures and the bone histology are highly suggestive for osteomalacia. The biochemical profile is characterized by an impressive

reduction of serum phosphorus level and an elevated urinary phosphate excretion related to a low tubular reabsorption of phosphate (TRP). Serum calcium in the normal range or slightly decreased, high serum bone alkaline phosphatase and a deficiency of  $1,25(\text{OH})_2\text{D}_3$  are typical biochemical features as well. Serum levels of  $25(\text{OH})\text{D}_3$  and PTH are usually in the normal range.

The tumors responsible for oncogenic osteomalacia have been described as 'strange tumors in strange places' (9); these neoplasms are often small in size (1 to 7 cm), and are commonly located in the bone or soft tissues of the lower extremities and craniofacial regions. About 40% of these tumors are vascular, with hemangiopericytoma features being the most common. Although most tumors are benign, several malignant cases have been reported (10, 11). The way in which these tumors lead to hypophosphatemia is not yet understood. Useful observations have come from the study of X-linked hypophosphatemic rickets (HYP), which is phenotypically similar to TIO. Although there are some differences in clinical presentation, both diseases are characterized by an excess in circulating phosphatonin which inhibits sodium-dependent phosphate reabsorption in the kidney and decreases 1 $\alpha$ -hydroxylase activity, resulting in hypophosphatemia and reduced  $1,25(\text{OH})_2\text{D}_3$  levels. Excess of phosphatonin in HYP is due to impaired degradation caused by mutation in the gene PHEX, which encodes for the endopeptidase responsible for phosphatonin catabolism. In TIO a large amount of phosphatonin, overwhelming endogenous PHEX activity, is likely to be generated by the tumor itself (12-14). Phosphatonin is a low molecular weight (8-25 KD) heat sensitive substance (15); its inactivation by trypsin supports a likely peptide structure (16). Recent studies suggest

that FGF-23 (a member of the fibroblast growth factor family that is overexpressed in tumors associated with TIO) could be identified with phosphatonin (17).

The diagnostic challenge is related to the identification of these insidious neoplasms. In several patients TC scan did not identify the tumor (18) and MRI scan, especially the whole-body one, is an expensive method and not always a certain diagnostic tool.

The discovery of somatostatin receptors on mesenchymal tumors have disclosed a new diagnostic path. Somatostatin receptors have been found in many normal tissues such as the gastrointestinal tract, central nervous system, anterior pituitary gland, endocrine and exocrine pancreas, activated immune cells, but have also been observed in high concentration in human neuroendocrine tumours stemming from the neural crest. Five different subtypes of somatostatin receptors have been identified: the subgroups 2, 3 and 5 show a high responsiveness to a somatostatin analogue such as octreotide (4). In this regard, the  $^{111}\text{In}$ -pentetreotide body scan can be considered a useful tool not only for detecting these tumors, but also for a therapeutic approach. As demonstrated in this case, scintiscan using radiolabelled somatostatin analogues can play a pivotal role in detecting a mesenchymal tumor related to an osteomalacia that is inexplicable in other way (4, 5).

## References

- DREZNER MK: Tumor-induced rickets and osteomalacia. In FAVUSMJ (Ed.): *Primer on the Metabolic Bone Diseases and Disorders of Mineral Metabolism*. New York, Raven Press 1996: 319-25.
- HEWISON M: Tumor-induced osteomalacia. *Curr Opin Rheumatol* 1994; 6: 340-4.
- REUBI JC, WASER B, LAISSUE JA, GEBBERS J: Somatostatin and vasoactive intestinal peptide receptors in human mesenchymal tumors *in vitro* identification. *Cancer Res* 1996; 56: 1922-31.
- SLOOTER GD, MEARADJI A, BREEMAN WA *et al.*: Somatostatin receptor imaging, therapy and new strategies in patients with neuroendocrine tumours. [Review] *Br J Surg* 2001; 88: 31-40.
- BALON HR, GOLDSMITH SJ, SIEGEL BA, KRENNING EP, LANG O, DONDHOE KJ: Procedure guideline for somatostatin receptor scintigraphy with  $^{111}\text{In}$ -pentetreotide. *J Nucl Med* 2001; 42: 1134-8.
- RHEE Y-L, LEE J-D, SHIN K-H, LEE H-C, HUH K-B, LIM S-K: Oncogenic osteomalacia associated with mesenchymal tumour detected by indium-111 octreotide scintigraphy. *Clin Endocrinol* 2001; 54: 551-4.
- MCCANCE RA: Osteomalacia with Looser's nodes (Milkman's syndrome) due to a raised resistance to vitamin D acquired about the age of 15 years. *Q J Med* 1947; 16: 33-46.
- PRADER VA, ILLIG R, VEHLINGER E, STALDER G: Rachitis, infolge, knochen tumors. *Helv Paediatr Acta* 1959; 14: 554-65.
- WEISS D, BAR RS, WEIDNER N, WENER M, LEE F: Oncogenic osteomalacia: Strange tumors in strange places. *Post-graduate Med J* 1985; 61: 349-55.
- OGOSE A, HOTTA T, EMURA I *et al.*: Recurrent malignant variant of phosphaturic mesenchymal tumor with oncogenic osteomalacia. *Skeletal Radiol* 2001; 30: 99-103.
- JOHN MR, WICKERT H, ZAAR K *et al.*: A case of neuroendocrine oncogenic osteomalacia associated with a PHEX and fibroblast growth factor-23 expressing sinusoidal malignant schwannoma. *Bone* 2001; 4: 393-402.
- NELSON AE, ROBINSON BG, MASON RS: Oncogenic osteomalacia: Is there a new phosphate regulating hormone? *Clin Endocrinol* 1996; 47: 635-42.
- THE HYP CONSORTIUM: A gene (PEX) with homologies to endopeptidases is mutated in patients with X-linked hypophosphatemic rickets. *Nature Genet* 1995; 11: 130-6.
- HOLM IA, HUANG X, KUNKEL LM: Mutational analysis of the PEX gene in patients with X-linked hypophosphatemic rickets. *Am J Hum Genet* 1997; 60: 790-7.
- CAI Q, HODGSON SF, KAO PC *et al.*: Inhibition of renal phosphate transport by a tumor product in a patient with oncogenic osteomalacia. *N Engl J Med* 1994; 330: 1645-9.
- NELSON AE, NAMKUNG HJ, PATAVA J *et al.*: Characteristics of tumor cell bioactivity in oncogenic osteomalacia. *Mol Cell Endocrinol* 1996; 124: 17-23.
- BOWE AE, FINNEGAN R, JAN DE BEUR SM *et al.*: FGF-23 inhibits renal tubular phosphate transport and is a PHEX substrate. *Biochem Biophys Res Comm* 2001; 284: 977-81.
- KAWAI Y, MORIMOTO S, SAKAGUCHI K *et al.*: Oncogenic osteomalacia secondary to nasal tumor with decreased urinary excretion of cAMP. *J Bone Miner Metab* 2001; 19: 61-4.