

Tumor-induced hypophosphatemic osteomalacia associated with tertiary hyperparathyroidism: a case report

F. TARTAGLIA, S. MINISOLA, M. SGUEGLIA, S. BLASI, D. BRUNELLI, E. DEGLI EFFETTI, A. MATURO, A. COLA, F. CUSTURERI, F.P. CAMPANA

SUMMARY: Tumor-induced hypophosphatemic osteomalacia associated with tertiary hyperparathyroidism: a case report.

F. TARTAGLIA, S. MINISOLA, M. SGUEGLIA, S. BLASI, D. BRUNELLI, E. DEGLI EFFETTI, A. MATURO, A. COLA, F. CUSTURERI, F.P. CAMPANA

Background. Tumor-induced hypophosphatemic osteomalacia is a syndrome characterized by urinary phosphate wasting related to the presence of a slowly-growing tumor of mesenchymal origin. The characteristic laboratory findings are normal serum calcium, marked hypophosphatemia, increased serum alkaline phosphatase, markedly reduced renal tubular reabsorption of phosphorus and inappropriately low levels of 1,25-dihydroxyvitamin D [1,25-(OH)₂D].

Case presentation. A 65-year-old woman presented with a 17-year clinical history of musculoskeletal pain, muscular weakness in the pelvic girdle, spontaneous fractures and difficulty in walking. Over the ensuing years the patient suffered other multiple spontaneous fractures, surgically treated, and the muscular pains worsened until she became bedridden. During the years before hospital admission the patient received treatment with clodronate, oral calcium salts and vitamin D therapy. Standard laboratory, ultrasonography and scintigraphic findings provided a "convenient" diagnosis of primary hyperparathyroidism, but the low plasma level of phosphorus induced to perform an Indium¹¹¹-octreotide scintigraphy. Scintigraphy visualized an area of pathologic increased signal uptake in the left groin, consistent with a mass containing a high density of somatostatin receptors. After surgery, histologic examination and immunostaining of the resected specimen indicated an hemangiopericytoma. Nevertheless, the persistently low blood phosphorus level, in association with the increased serum calcium and PTH levels, were attributed to the prolonged phosphate therapy the patient underwent over the years, and the persisting abnormal laboratory indexes indicated the development of a tertiary hyperparathyroidism. We performed a subtotal parathyroidectomy and intraoperative assay of serum PTH showed that levels had diminished by more than 80% from preoperative values. Over the ensuing months Ca²⁺, PTH and serum phosphorus values returned to normal, and the pain symptoms disappeared.

Conclusions. Tumour-induced osteomalacia is a very rare syndrome associated in 5% of cases with tertiary hyperparathyroidism due to long-term therapy with phosphorus and vitamin D.

The initial diagnosis of primary hyperparathyroidism, confirmed by the parathyroid MIBI-scintigraphy, would lead us to an inappro-

RIASSUNTO: Osteomalacia ipofosfatemica oncogenica associata a iperparatiroidismo terziario: case report.

F. TARTAGLIA, S. MINISOLA, M. SGUEGLIA, S. BLASI, D. BRUNELLI, E. DEGLI EFFETTI, A. MATURO, A. COLA, F. CUSTURERI, F.P. CAMPANA

Introduzione. L'osteomalacia ipofosfatemica oncogenica è una sindrome caratterizzata da una perdita urinaria di fosfati determinata da un tumore mesenchimale a lenta crescita. Gli esami di laboratorio documentano calcemia normale, marcata ipofosfatemica, incremento della fosfatasi alcalina sierica, notevole riduzione del riassorbimento renale tubulare di fosforo ed una inappropriata bassa concentrazione nel siero di 1,25-diidrossi-vitamina D [1,25-(OH)₂D].

Caso clinico. Donna di 65 anni, da 17 anni sofferente di dolori muscoloscheletrici, astenia muscolare in particolare del cingolo pelvico, fratture spontanee multiple trattate chirurgicamente e difficoltà nella deambulazione. Attualmente allettata per progressiva ingravescenza dei dolori muscolari, la paziente era da anni in terapia con clodronato e supplementi di calcio e vitamina D. Gli esami di laboratorio e strumentali 'standard' (ultrasonografia, scintigrafia) deponevano per iperparatiroidismo primario, ma i bassi livelli di fosforo suggerivano un approfondimento diagnostico con una scintigrafia con octreotide Indium¹¹¹-marcata, che evidenziava un uptake patologico del marcatore in regione inguinale sinistra, compatibile con la presenza di una formazione ad alta densità di recettori per la somatostatina. La paziente veniva pertanto sottoposta ad intervento chirurgico di asportazione della formazione inguinale, il cui esame istologico ed immunoistochimico deponeva per emangiopericitoma. La persistenza postoperatoria di bassi livelli ematici di fosforo, associati a concentrazioni sieriche elevate di calcio e PTH, era attribuita alla pregressa terapia cronica con fosfati (di calcio). Le alterazioni dei parametri di laboratorio indicavano la comparsa di un iperparatiroidismo terziario. Si decideva pertanto per una paratiroidectomia subtotale. La determinazione intraoperatoria dell'PTH sierico dimostrava un riduzione di oltre l'80% dei livelli preoperatori. Nei mesi successivi si normalizzavano anche i valori sierici di Ca²⁺ e fosforo con risoluzione della sintomatologia dolorosa.

Conclusioni. L'osteomalacia oncogenica è una sindrome molto rara associata nel 5% dei casi ad iperparatiroidismo terziario indotto da una terapia protratta con fosfati e vitamina D. La diagnosi iniziale di iperparatiroidismo primario, apparentemente confermata dalla

priate surgical treatment. Therefore we want to stress the importance of In^{111} -octreotide scintigraphy in detecting tumours, rich in somatostatin receptors, in presence of an hypophosphatemic syndrome.

MIPI-scintigrafia paratiroidea, può portare ad un intervento chirurgico inappropriato. Si sottolinea pertanto l'importanza della In^{111} -octreotide scintigrafia per la individuazione di un possibile tumore ad alta densità di recettori per la somatostatina responsabile della sindrome ipofosfatemica.

KEY WORDS: Hypophosphatemia - Tumor-induced osteomalacia - Tertiary hyperparathyroidism - Imaging - Surgery.
Ipofosfatemia - Osteomalacia oncogena - Iperparatiroidismo terziario - Imaging - Chirurgia.

Background

Tumor-induced hypophosphatemic osteomalacia, a syndrome rarely reported in the medical literature, is characterized by urinary phosphate wasting related to the presence of a slowly-growing bone or soft-tissue tumor of mesenchymal origin that is often difficult to discover. The syndrome affects adults of both sexes; despite peak incidence in the fourth decade, the causative tumor often remains unrecognized until the fifth or sixth decades of life (1, 2).

Although hypophosphatemic osteomalacia was first described by McCance in 1947 (3), and later by Prader in 1959 (4), the causative tumors were categorized by Weidner (5) and Santa Cruz only in 1987. The most frequent are giant cell osteoblastomas, hemangiomas, fibromas, hemangiopericytomas, fibroangiomas, osteoblastomas, chondromas, chondroblastomas, fibrous xanthomas but the syndrome arises also from prostate carcinomas, "oat cell" carcinomas, sarcomas, malignant histiocytic histiocytomas, neurinomas, multiple myeloma and neurofibromatosis.

The characteristic laboratory findings are normal serum calcium, marked hypophosphatemia, increased serum bone alkaline phosphatase, markedly reduced renal tubular reabsorption of phosphorus and inappropriately low levels of 1,25-dihydroxyvitamin D [1,25-(OH)₂D].

The mechanism underlying this rare syndrome is thought to involve humoral factors produced by the causative neoplasm, called "phosphatonins". In a study conducted in 2001, Shimada et al. (6) identified phosphatonin as a member of the FGF (Fibroblast Growth Factors) family, namely FGF-23. This growth factor, secreted also by normal tissues, appears to have a central role as a hormone regulator of phosphate metabolism. Owing to overproduction, FGF-23 abundantly expressed by neoplastic tissues appears to induce the hyperphosphaturia syndrome by inhibiting renal tubular reclamation of phosphorus.

Besides FGF-23, the phosphatonin group comprises other factors including frizzled-related protein 4 (FRP-4) and matrix extracellular phosphoglycoproteins (MEPE), putatively involved in regulating bone mineralization. All three proteins acting synergically

or sequentially might reasonably intervene in hypophosphatemia. Both factors are invariably elevated in patients with tumor-induced osteomalacia and after surgical removal of the responsible tumor diminish as the pain symptoms and functional weakness regress (7, 8).

We present the case of an adult woman with tumor-induced hypophosphatemic osteomalacia caused by a hemangiopericytoma in the left groin. Prolonged phosphate therapy over the patient's 17-year clinical history led to the development of tertiary hyperparathyroidism thus preventing plasma phosphorus levels from normalizing even after surgical removal of the tumor.

Case presentation

A 65-year-old woman presented with a 17-year clinical history of musculoskeletal pain, muscular weakness in the pelvic girdle and difficulty in walking. X-ray films obtained at the age of 52 showed symmetric fractures involving the iliac and ischiopubic branches. A bone-biopsy specimen yielded a diagnosis of "osteomalacia". Therapy was started with calcium, vitamin D and phosphates.

Over the ensuing years the patient suffered other multiple spontaneous fractures surgically treated (right and left femur, right humerus and the proximal third of the first and second metacarpal bones in the right hand) and the muscular pains worsened until she became bedridden. During the years before hospital admission the patient received treatment with clodronate (bisphosphonate) and oral administration of calcium salts and vitamin D.

Standard diagnostic radiographs on admission documented the previous fractures. Radiographs of the cranium and sella turcica and X-ray mammography gave normal findings. A bone density scan showed severe osteoporosis. Total body magnetic resonance imaging (MRI) showed multiple small areas of increased signal on T₂-weighted images and areas of decreased signal on T₁-weighted sequences (previous fractures?; myelomatosis lesions?). Laboratory findings included a negative Bence-Jones test for proteinuria thus excluding a diagnosis of myeloma and con-

firming that the MRI documented lesions originated from trauma. Laboratory measurements of serum electrolytes, creatinine, glucose, urea nitrogen, white blood cell count and coagulation were normal, as were serum erythrocyte sedimentation rate, electrophoresis, immunoelectrophoresis, immunoglobulin assay, and acid-base equilibrium. Despite a normal total serum calcium concentration the following indexes were abnormal: ionized calcium (Ca^{2+}) was high; phosphorus was very low; alkaline phosphatase and bone alkaline phosphatase were high; parathyroid hormone values (PTH) was twice normal; 1,25-(OH) $_2$ D was low. Conversely, levels of 25-hydroxyvitamin D [25-(OH)D], the active vitamin D precursor, were normal.

An ultrasound scan of the neck, obtained to investigate suspected primary hyperparathyroidism, disclosed a hypoechoic area measuring about 0.6 cm in maximum diameter posterior to the left thyroid lobe, initially attributed to a parathyroid gland. Parathyroid scintigraphy showed increased Technetium^{99m}-MIBI uptake in correspondence with the left inferior thyroid lobe, consistent with a parathyroid adenoma. These scintigraphic findings along with the suspected primary hyperparathyroidism nevertheless seemed not to justify the patient's poor clinical conditions, especially considering the almost normal findings on ultrasonography, serum PTH values only twice normal and most important, the exceedingly low serum phosphorus associated with low serum vitamin D levels, elevated alkaline phosphatase and a normal total serum calcium concentration.

These findings led our endocrinologists to suspect hypophosphatemic osteomalacia, a suspicion confirmed by a literature review underlining its frequent association with mesenchymal neoplasms. The patient therefore underwent Indium¹¹¹-octreotide scintigraphy because recent studies have identified somatostatin receptors in mesenchymal neoplasias (9). Scintigraphy readily and quickly visualized an area of pathologic increased signal uptake at a site corresponding to the left groin, consistent with a mass containing a high density of somatostatin receptors.

Spiral computed tomographic (CT) scanning targeting the scintigraphic findings disclosed an oval expanding lesion (4 cm in diameter) with evident contrast enhancement within the left groin, sited deeply to the femoral muscle insertion and externally to the femoral vessels (Fig. 1). Surgery for removal disclosed within the left groin a roundish, yellowish mass with a variegated appearance and soft consistency; the mass measured 5x6x3 cm and adhered closely to the surrounding tissues (Fig. 2). Histologic examination of the resected specimen indicated a mesenchymal tumor. Tumor cells stained strongly positive

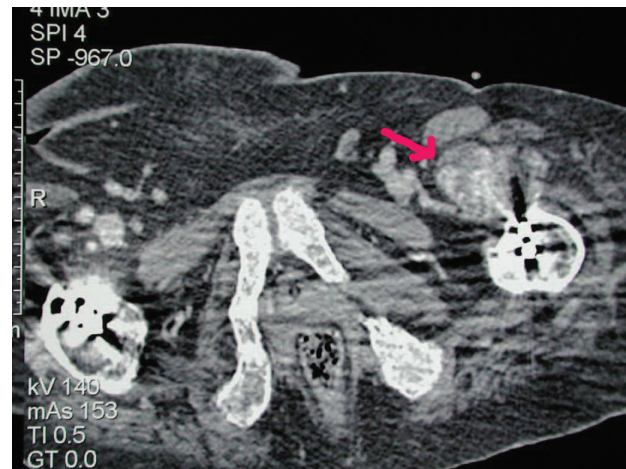


Fig. 1 - Spiral computed tomographic scan showing an oval expanding lesion (4 cm in diameter) with evident contrast enhancement within the left groin, sited deeply to the femoral muscle insertion and externally to the femoral vessels. Artefacts by hip prosthesis.

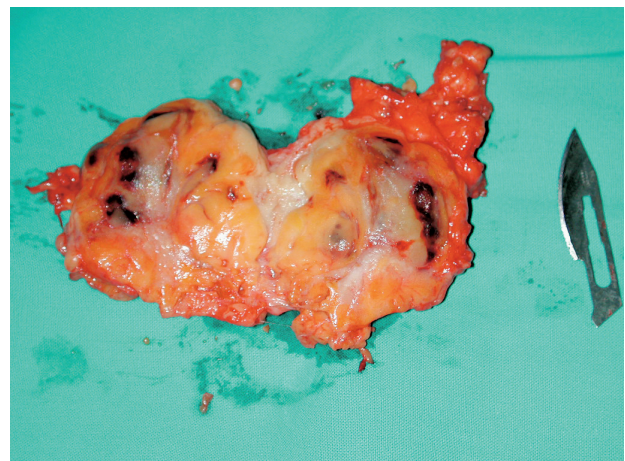


Fig. 2 - Operative specimen. Histologic examination indicated a mesenchymal tumor. Immunostaining indicated a diagnosis of hemangiopericytoma.

for vimentin and neuron-specific enolase but were negative for cytokeratin, S-100 and synaptophysin immunostaining therefore indicating a diagnosis of hemangiopericytoma.

One week after surgery, without therapy, serum phosphorus values nearly doubled then stabilized and the pain symptoms improved, but PTH levels remained high. Assay of fibroblast growth factor type 23 (FGF-23), that preoperatively showed high values, progressively became negative.

Over the ensuing months the patient underwent cycles of therapy with calcitriol and phosphorus; even though the symptoms markedly improved, serum phosphorus values never returned to normal ranges but remained low. At the same time, Ca^{2+} and PTH increased.

The persistently low blood phosphorus level, albeit less marked than the preoperative decrease, in

association with the increased serum calcium and PTH levels, were attributed to the prolonged phosphate therapy the patient underwent over the years, hence to secondary hyperparathyroidism associated with chronic parathyroid stimulation. Even though phosphate supplementation was suspended, the persisting abnormal laboratory indexes indicated the development of autonomous parathyroid dysfunction, hence a form of tertiary hyperparathyroidism.

Surgical exploration of the neck showed that both left parathyroid glands and the inferior right parathyroid gland were enlarged and were removed. The upper left parathyroid gland appeared normal in size and was left in situ. Histological frozen sections confirmed diffuse hyperplasia. Intraoperative assay of serum PTH showed that levels had diminished by more than 80% from preoperative values allowing subtotal parathyroidectomy.

Over the ensuing months Ca^{2+} and PTH values returned to normal, serum phosphorus rose to normal value and the pain symptoms and muscle weakness progressively improved until the patient was again able to walk.

Conclusions

Tertiary hyperparathyroidism associated with hypophosphaturic osteomalacia has rarely been reported in the literature (10-12) and complicates no more than 5% of the cases (13, 14). The distinctive feature in this patient was the unexpected finding of a mesenchymal tumor in a patient with suspected primary hyperparathyroidism, a diagnosis that would have led to inappropriate surgical treatment. In our case the correct diagnosis, tumor-induced hypophosphatemic osteomalacia, was suggested by preoperative assay of FGF-23, and confirmed by Indium¹¹¹-octreotide scintigraphy.

As is typical of patients with hypophosphoremic osteomalacia, our patient had a 17-year history of severe muscle weakness and pain before tumor-

induced hypophosphatemic osteomalacia was diagnosed. Even though published reports (15) number more than 100 patients since McCance first described the disorder, because the syndrome is little known the diagnosis can be delayed even 20 years after the first symptoms manifest (14). Even though the preceding diagnostic imaging (neck ultrasonography and parathyroid scintigraphy) provided a "convenient" diagnosis of primary hyperparathyroidism, the turning point came when octreotide scintigraphy undertaken to explain the concomitant biochemical humoral changes detected the mesenchymal tumor. Once the primary tumor was removed, plasma FGF-23 almost halved but blood phosphorus values, despite a marked increase, never came within the normal range, indicating that the phosphaturic stimulus persisted. Given the patient's clinical history and her continued phosphate treatment for many years we therefore attributed this residual phosphaturia to tertiary hyperparathyroidism.

Phosphates act directly by sequestering calcium thus stimulating parathyroid glands. In our case, chronic parathyroid stimulation led to hyperplasia followed by autonomous parathyroid gland hyperfunction thereby worsening renal phosphate wasting. The tertiary hyperparathyroidism prevented the complete normalization of serum phosphorus levels.

The operative confirmation of multiple hyperplasia and the rapid assay for measuring serum PTH during surgery, a technique we consider indispensable in these cases, allowed us to remove the hyperphosphaturic stimulus, without recourse to total parathyroid gland ablation. After surgery blood and urine indexes returned to normal and the patient regained the use of her arms and legs, and resumed normal relationships.

Because mesenchymal tumors of this type tend to recur, often owing to incomplete removal (16), multicentric disease (17) or metastatic disease (14), these patients should undergo long-term surveillance including regular laboratory testing and diagnostic imaging.

References

1. Weidner N. Review and update: oncogenic osteomalacia-rickets. *Ultrastruct Pathol* 1991; 15: 317-33.
2. Schapira D, Izhak OB, Nachtigal A, Burstein A, Shalom RB, Shagrawi I, Best LA. Tumor-induced osteomalacia. *Semin Arthritis Rheum* 1995; 25: 35-46.
3. McCance RA. Osteomalacia with Looser's nodes (Milkman's syndrome) due to the raised resistance to vitamin D acquired about the age of 15 years. *Q J Med* 1947; 16: 33-47.
4. Prader A, Illig R, Uehlinger RE, Stalder G. Rickets caused by bone tumors. *Helv Paediatr Acta* 1959; 14: 554-65.
5. Weidner N, Santa Cruz D. Phosphaturic mesenchymal tumors: a polymorphous group causing osteomalacia or rickets. *Cancer* 1987; 59: 1442-54.
6. Shimada T, Mizutani S, Muto T, Yoneya T, Hino R, Takeda S, Takeuchi Y, Fujita T, Fukumoto s, Yamashita T. Cloning and characterization of FGF23 as a causative factor of tumor-

- induced osteomalacia. *Proc Natl Acad Sci USA* 2001; 98: 6500–5.
7. Schiavi SC, Kumar R. The phosphatonin pathway: new insights in phosphate homeostasis. *Kidney Int* 2004; 65 (1): 1-14.
 8. Jan de Beur SM, Finnegan RB, Vassiliadis J et al.: Tumors associated with oncogenic osteomalacia express genes important in bone and mineral metabolism. *J Bone Miner Res.*, 2002; 17: 1102-10.
 9. Rhee Y, Lee JD, Shin KH, Lee HC, Huh KB, Lim SK. Oncogenic osteomalacia associated with mesenchymal tumour detected by indium-111 octreotide scintigraphy. *Clin. Endocrinol (Oxf)* 2001; 54 (4): 551-4.
 10. Jeon HJ, Kwon SH, Kim SW, Shin CS, Park KS, Kim SY, Cho BJ, Lee HK. Evaluation of the parathyroid function in six patients with hypophosphatemic osteomalacia, including a case of tertiary hyperparathyroidism developing during combined oral phosphate and vitamin D therapy. *Horm Res*; 2003; 60 (3): 127-33.
 11. Huang QL, Feig DS, Blackstein ME. Development of tertiary hyperparathyroidism after phosphate supplementation in oncogenic osteomalacia. *J Endocrinol Invest* 2000; 23 (4): 263-7.
 12. Younis E, Jarrah N, Sroujeh AS, Al Hadidy A, Ajlouni K. Tertiary hyperparathyroidism after high-dose phosphate therapy in adult-onset hypophosphatemic osteomalacia. *Endocr Pract* 2001; 7 (5): 375-8.
 13. Stamp TCB. The clinical endocrinology of vitamin D. In: Parsons J.A., ed. *Endocrinology of calcium metabolism*. New York: Raven Press, 1982: 396–7.
 14. Drezner MK. Oncogenic rickets and osteomalacia. In: Favus M.J., ed. *Primer on the metabolic bone diseases and disorders of mineral metabolism*, 3rd edn. Philadelphia: Lippincott-Raven, 1996: 319–25.
 15. Folpe AL, Fanburg-Smith JC, Billings SD, Bisceglia M, Bertoni F, Cho JY, Econs MJ, Inwards CY, Jan de Beur S.M., Mentzel T, Montgomery E, Michal M, Miettinen M, Mills SE, Reith JD, O'Connell JX, Rosenberg AE, Rubin BP, Sweet DE, Vinh TN, Wold LE, Wehrli BM, White KE, Zaino RJ, Weiss SW. Most osteomalacia-associated mesenchymal tumors are a single histopathologic entity: an analysis of 32 cases and a comprehensive review of the literature. *Am J Surg Pathol* 2004; 28 (1): 1-30.
 16. Clunie GP, Fox PE, Stamp TC. Four cases of acquired hypophosphataemic ('oncogenic') osteomalacia. Problems of diagnosis, treatment and long-term management. *Rheumatology (Oxford)* 2000; 39 (12): 1415-21.
 17. Becker W, Stosiek N, Peters KP, Wolf F. Bone scan and red blood cell scan in a patient with epidermal naevus syndrome. *Eur J Nucl Med* 1990; 17: 369-71.