Oncogenic Osteomalacia

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Oncogenic osteomalacia is a rare cause of hypophosphatemia and osteomalacia, and is usually associated with mesenchymal tumors [1–4] and rarely with carcinoma of the prostate [5]. The condition may be difficult to diagnose, since osteomalacia presents with bone pain and functional disability that may already be present in cases of prostatic carcinoma with multiple bony metastases. If attention is not paid to the development of hypophosphatemia the diagnosis may be missed. I describe here a case of osteogenic osteomalacia associated with prostatic carcinoma and discuss the pathophysiology of this condition.

Case Description

A 77 year old man was found in February 1998 to have an elevated prostate-specific antigen level of 860 ng/ml. Rectal examination revealed an enlarged prostate containing several hard nodules, and prostatic biopsy disclosed adenocarcinoma. A bone scan demonstrated many pathological foci in the skull, ribs, spine, pelvis and femurs, compatible with multiple bone metastases. X-rays showed multiple lytic and blastic lesions and generalized osteopenia. He was treated initially with flutamide, which was stopped because of hepatotoxicity, and subsequently with goserelin, aminoglutethimide and glucocorticoids. However, he continued to suffer from severe bone pain and weakness that progressively worsened.

Two months later hypophosphatemia of 1.8 mg/dl was noted for the first time [Figure 1]. At this point the PSA had fallen to 261 ng/ml. By January 1999 phosphate had fallen to 1.1 mg/dl, with serum total calcium of 8.3 mg/dl. Further investigations were performed. Serum intact parathyroid hormone level was 65 ng/ml (normal 10–55). Serum 25-OH vitamin D_3 level was 10 ng/ml (normal 10–50), and $1,25(OH)_2$-vitamin D_3 level 8 pg/ml (normal 16–45). Renal phosphate excretion was then examined. Tubular reabsorption of phosphate was 60.5% (normal >85%), and TmP/GFR 0.7 mg/dl (normal 2.5–4.2) (calculated from the nomogram of Watson and Bijvoet, *Lancet* 1975;ii:309). These findings thus indicated a marked renal phosphate leak that was responsible for the hypophosphatemia. Therapy was begun with oral 1α-vitamin D_3 (2 μg/day) and sodium and potassium phosphate (1.8 g phosphate/day). Phosphate subsequently rose to between 2.0 and 2.7 mg/dl [Figure 1] until June 1999, when it fell again to 1.3 mg/dl. The αD3 and phosphate doses were increased. The patient suffered from constant severe bone pain and a pathological fracture of the hip. He was admitted to hospital in July and received pamidronate i.v. One week after this treatment, serum total calcium fell to 5.2 mg/dl, with the appearance of tetany. He was given i.v. calcium but died a few days later.

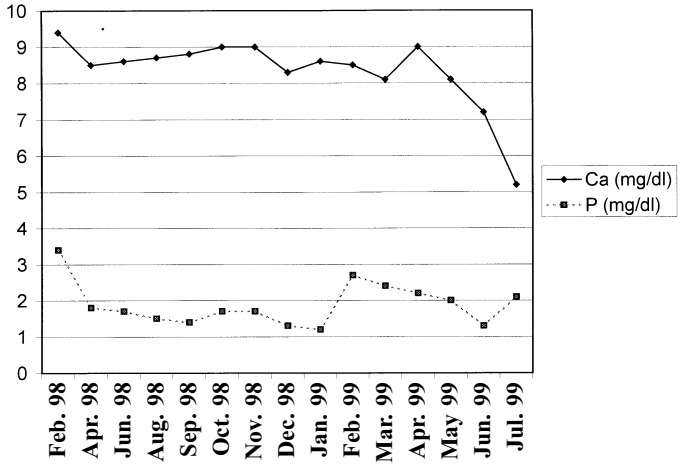

Figure 1. Serum total calcium and inorganic phosphate levels in a patient with oncogenic osteomalacia

Comment

Oncogenic (or tumor-induced) osteomalacia has been described in association with a number of tumors, notably mesenchymal tumors such as fibromas [1], hemangiomas [1,3], osteoblastomas [1], hemangiopericytomas [1,4], angiosarcomas [1], paraganglioma [2] and, less commonly, carcinoma of prostate [5]. The clinical picture consists of symptomatic osteomalacia, raised alkaline phosphatase, and hypophosphatemia, mainly due to a marked renal phosphate leak. In addition, plasma $1,25(OH)_2D3$ levels are low. The syndrome typically improves or disappears on removal of the tumor, which is most commonly benign and often difficult to detect since it is usually small and tends to occur in obscure areas [1].

The etiology of this syndrome is of considerable interest. Tumor-associated hypophosphatemia may be due to abnormal secretion of PTH or PTH-

PSA = prostate-specific antigen

PTH = parathyroid hormone

related peptide; or it may be associated with a putative phosphaturic substance, causing the syndrome of osteogenic osteomalacia. In syndromes associated with hypersecretion of PTH or PTHrp, the hypophosphatemia is always associated with hypercalcemia, which is never the case in osteogenic osteomalacia where calcium is always normal or slightly low. It was suspected for many years that these tumors secreted a phosphaturic substance that was probably neither PTH nor PTHrp. Wilkins et al. [2] described a patient with oncogenic osteomalacia due to a paraganglioma in the infratemporal fossa. The tumor was removed and all the biochemical abnormalities resolved over the next few months. The tumor cells were employed to establish a cell culture line, and a bioassay with the opossum kidney cells was used to evaluate phosphate transport. Conditioned medium from this cell culture inhibited phosphate reabsorption by the kidney tubular cells, and the inhibition was not affected by the presence of the protein inhibitor cycloheximide. An immunoassay did not reveal any detectable PTH or PTHrp in the medium, and thus neither PTH nor PTHrp was responsible for the inhibition of phosphate reabsorption. Cai et al. [3] cultivated sclerosing hemangioma cells from a patient with oncogenic osteomalacia and found that the medium inhibited sodium-dependent phosphate transport in opossum kidney epithelial cells, but did not increase intracellular cAMP levels and that its activity was not blocked by a PTH antagonist. The tumor cells thus secreted a humoral factor that inhibited renal phosphate reabsorption but was not PTH or PTHrp. The authors called this factor "phosphatonin." This factor also appears to cause the low levels of $1,25(OH)_2$-vitamin D_3 that are characteristic of this condition, as evidenced by the finding of Miyauchi and coworkers [4] that tumor extracts from a patient with oncogenic osteomalacia inhibited renal 25-OH-D_3 1-hydroxylase activity. The low levels of $1,25(OH)_2$-vitamin D_3 are important since they are probably a contributing factor to the renal phosphate losses.

Recently, important new findings were reported from studies on patients suffering from X-linked hypophosphatemic rickets in whom osteomalacia also developed because of a severe renal phosphate leak. In this condition the renal phosphate leak is due to a putative excess of phosphatonin, just as in oncogenic osteomalacia. The gene responsible on the X-chromosome was recently cloned and has been termed "PHEX" or PHosphate-regulating gene, with homologies to Endopeptidases located on the X-chromosome [6]. The phenotypic expression of XLH appears to be due to deactivating mutation of the PHEX gene. However, since this gene codes for a membrane-bound enzyme, it is clear that the PHEX protein is not phosphatonin, which is a circulating humoral factor. It appears likely that both phosphatonin and PHEX protein are produced by osteoblasts, and that PHEX protein is a membrane-bound endopeptidase responsible for degrading the hormone. In XLH, the mutant PHEX fails to inactivate sufficient phosphatonin, which is thus present in excess and causes massive renal phosphate loss. In oncogenic osteomalacia, the tumor itself produces massive amounts of phosphatonin, which exceed the capability of the PHEX to degrade sufficient amounts despite the fact that the PHEX may be present in increased amounts due to a presumed feedback mechanism. The vast amounts of phosphatonin cause greatly increased renal phosphate loss [7].

The PTH in our patient was moderately raised, probably in response to the mild hypocalcemia that was often seen. The reason for the hypocalcemia is not entirely clear, but could be explained by the very extensive blastic lesions, which if predominating over the lytic lesions could have caused a mild "hungry bones" syndrome. A comment should be made about the symptomatic hypocalcemia that appeared shortly before the patient died. This occurred a few days after he was given i.v. pamidronate for severe pain from the bone metastases. The bisphosphonates such as pamidronate inhibit osteoclast activity. The patient had many lytic and blastic metastases, and the effect of pamidronate would have inhibited the excess osteoclastic activity of the lytic metastases while leaving the excess osteoblastic activity of the blastic metastases unopposed – causing greatly increased bone uptake of calcium, and thus severe hypocalcemia. This possibility should be kept in mind when administering bisphosphonates to patients with multiple lytic and blastic metastases, and serum calcium levels should be carefully monitored for several days afterwards.

PTHrp = PTH related peptide

XLH = X-linked hypophosphatemic rickets

References

1. Ryan EA, Reiss E. Oncogenous osteomalacia. *Am J Med* 1984;77:501–12.
2. Wilkins GE, Granleese S, Hegele RG, Holden J, Anderson DW, Bondy GP. Oncogenic osteomalacia: evidence for a humoral phosphaturic factor. *J Clin Endocrinol Metab* 1995;80:1628–34.
3. Cai Q, Hodgson SF, Kao PC, Lennon VA, Klee GG, Zinsmeister AR, Kumar R. Brief report: inhibition of renal phosphate transport by a tumor product in a patient with oncogenic osteomalacia. *N Engl J Med* 1994;330:1645–9.
4. Miyauchi A, Fukase M, Tsutsumi M, Fujita T. Hemangiopericytoma-induced osteomalacia: tumor transplantation in nude mice causes hyperphosphaturia and tumor extracts inhibit renal 25-hydroxyvitamin D 1-hydroxylase activity. *J Clin Endocrinol Metab* 1988;67:46–53.
5. Reese DM, Rosen PJ. Oncogenic osteomalacia associated with prostate cancer. *J Urol* 1997;158: 887.
6. Rowe PSN, Goulding JN, Econs MJ, Francis F, Lehrach H, Read A, Mountford J, Oudet C, Hanauer A, Summerfield T, Meitinger T, Strom A, Drezner MK, Davies KE, O'Riordan JLH. The gene for X-linked hypophosphatemic rickets maps to a 200-300 kb region in Xp22.1–Xp22.2, and is located on a single YAC containing a putative vitamin D response element (VDRE). *Hum Genet* 1996;97:345–52.
7. Drezner MK. PHEX gene and hypophosphatemia. *Kidney Int* 2000;57:9–18.

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