Hypocalcemia Due to Avid Calcium Uptake by Osteoblastic Metastases of Prostate Cancer

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A THIRD OF PATIENTS WITH prostate cancer and bone metastases have a low serum calcium concentration,[1-3] and some have severe hypocalcemia. One mechanism, avid calcium uptake by osteoblastic bone metastases, was postulated more than 30 years ago.[4] When we reviewed the literature, however, we could not find any cases we thought were adequately documented.

Herein we describe the case of a patient with hypocalcemia and prostate cancer with diffuse osteoblastic metastatic involvement of the entire rib cage and spine. Clinical investigation provided for the first time overwhelming evidence that hypocalcemia was caused by avid calcium uptake by the osteoblastic metastases.

Report of a Case

The patient, an 82-year-old man with an indwelling Foley catheter, lived in a nursing home because of dementia. In December 1992, he was sent to Meridia Huron Hospital (Cleveland, Ohio) because of decreasing appetite, increasing lethargy, fever, and mild shortness of breath of a few days' duration. His temperature was 38°C, blood pressure 146/96 mm of mercury, heart rate 92 beats per minute, and respiratory rate 28 per minute. He was disoriented, lethargic, and cachectic. The lungs on examination were unremarkable. There was a 1-cm decubitus ulcer on the buttock. A firm nodule was felt in the right lobe of the prostate.

On admission, the following laboratory test values were elicited: serum calcium, 1.67 mmol per liter (6.7 mg per dl); phosphorus, 1.07 mmol per liter (3.3 mg per dl); alkaline phosphatase, 1,023 U per liter (normal, 37 to 107); albumin, 27 grams per liter; total protein, 59 grams per liter; urea nitrogen, 12.1 mmol per liter (34 mg per dl); creatinine, 110 μmol per liter (1.2 mg per dl); and magnesium, 0.95 mmol per liter (normal, 0.66 to 0.99). A serum sodium level was 152, potassium 4.6, bicarbonate 25, and chloride 113 mmol per liter. A serum glucose level was 7.7 mmol per liter (139 mg per dl), and an aspartate aminotransferase level was 44 U per liter (normal, 12 to 45). His hemoglobin level was 70 grams per liter; mean corpuscular volume, 89 fl; leukocyte count, 8.1×10^9 per liter; and platelet count, 261×10^9 per liter. Proteinuria (1.0 gram per liter) and moderate hematuria were found on urinalysis, and the urine sediment contained 11 to 25 leukocytes and many bacteria per high-power field, although nitrite and leukocyte esterase were not detected. The initial evaluation suggested dehydration and urinary tract infection, and a regimen of intravenous fluids and antibiotics was started.

Studies were done to identify the cause of hypocalcemia and the extremely elevated alkaline phosphatase level. An acid phosphatase level was 68 U per liter (normal, 0 to 5.7); prostate-specific antigen, 665 μg per liter (normal, 0 to 4.0); ionized calcium, 0.90 mmol per liter (3.6 mg per dl; normal, 1.15 to 1.35 mmol per liter; performed by the Nichols Institute [San Juan Capistrano, California], ion-specific electrode); urinary calcium, 0.3 mmol (12 mg) per 24 hours; intact (immunoradiometric assay) parathyroid hormone, 95 ng per liter (performed by the Nichols Institute; normal, 10 to 65 ng per liter), when the serum calcium level was 1.6 mmol per liter (6.5 mg per dl); serum 25-hydroxyvitamin D, 180 nmol per liter (normal, 22 to 130); and 1,25-dihydroxyvitamin D, 247 pmol per liter (normal, 36 to 144). Other studies included a serum vitamin B_{12} level, 630 pmol per liter (normal, 180 to 920); folic acid, 58 nmol per liter (normal, 6 to 49); and ferritin, 1,760 μg per liter (normal, 30 to 300). X-ray films showed a striking diffuse increase in opacity of the entire rib cage and spine since previous x-ray films, consistent with an osteoblastic process. A prostatic biopsy showed moderately differentiated adenocarcinoma.

The patient died two weeks after admission. Postmortem random needle biopsies of rib and iliac crest confirmed the presence of diffuse metastatic adenocarcinoma. The presence of many osteoblasts and increased trabecular matrix were consistent with new bone formation.

Discussion

A low serum total calcium concentration has been reported in 14% of all patients with carcinoma of the prostate and in 23% to 32% of those with bone metastases.[1-3] Usually this is due to hypoalbuminemia; true hypocalcemia, defined as a low ionized calcium concentration, is much less common, occurring in about 2% of all cases of prostate cancer.[3] Even so, prostate cancer is a common disease; 165,000 new cases were expected in the United States in 1993.[5] Thus, we should expect about 3,300 patients per year to have true hypocalcemia and a much larger number to have a low total calcium concentration. In view of these estimates, we were surprised to find a paucity of articles dealing with the pathogenesis of hypocalcemia in patients with prostatic cancer.

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True hypocalcemia can develop in various ways. Because many of these patients are old and have other medical problems, causes of hypocalcemia unrelated to prostate cancer itself must be considered. The most common of these is renal failure, and others include hypomagnesemia and malabsorption.

There are several ways in which hypocalcemia might be due directly to prostate cancer metastatic to bone. One mechanism might be impaired 1α-hydroxylation, leading to low levels of 1,25-dihydroxyvitamin D. This has been well documented in certain connective tissue tumors[6] and in two cases of prostate cancer.[7]

Avid uptake of calcium by osteoblastic metastases of prostate cancer was postulated as a cause of hypocalcemia in three patients whose cases were reported individually.[3,8,9] Such patients would be expected to have secondary hyperparathyroidism and, as a consequence, a low or low-normal serum phosphorus level and an elevated or high-normal serum 1,25-dihydroxyvitamin D concentration. Furthermore, the absence of other possible causes of hypocalcemia would make avid uptake by osteoblastic metastases more likely as the sole cause of hypocalcemia. Unfortunately, none of the patients in the cases previously reported met all these conditions.

The serum parathyroid hormone level was slightly elevated in one reported case,[8] but the high serum phosphorus and low 1,25-dihydroxyvitamin D concentrations suggest resistance to parathormone. Another patient had an increased serum parathormone concentration, but the 1,25-dihydroxyvitamin D concentration was not measured,[9] and the serum 25-hydroxyvitamin D level was at the lower limit of normal. The third patient had a normal serum parathormone concentration despite mild chronic renal insufficiency, possibly because of hypomagnesemia, and a serum 1,25-dihydroxyvitamin D level was near the lower limit of normal.[3] In fact, calcium malabsorption due to vitamin D deficiency, relatively low levels of 1,25-dihydroxyvitamin D, or both, probably played a role in all three of these patients.

In our patient, both total and ionized serum calcium levels were low, documenting true hypocalcemia. The serum magnesium concentration was well within normal limits. Clinically important renal insufficiency was not present; the serum creatinine level was only marginally elevated, and there was no phosphorus retention. Hypercalciuria was excluded.

Our patient's elevated parathormone and 1,25-dihydroxyvitamin D concentrations indicated a normally functioning regulatory mechanism, although higher values might have been expected for this degree of hypocalcemia. Because we thought one of the previously reported patients might have had peripheral resistance to parathormone,[8] we considered this possibility in our patient; the low-normal serum phosphorus and elevated 1,25-dihydroxyvitamin D levels provided good evidence against this. We did not measure the urinary phosphorus excretion, so we cannot exclude some blunting of the phosphaturic response to parathormone.

The normal vitamin B_{12} and folate concentrations and the high serum ferritin level provide evidence against generalized malabsorption. The elevated concentration of 1,25-dihydroxyvitamin D provides evidence against calcium malabsorption or tumor-related impairment of 1α-hydroxylation. Furthermore, calcium malabsorption could not explain the generalized increase in bone opacity seen on x-ray films.

In summary, this case provides convincing evidence that avid uptake of calcium by osteoblastic metastases can cause true hypocalcemia in patients with prostatic cancer.

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