Clinical Investigation

Tumoral Calcification: Evidence for Concurrent Defects in Renal Tubular Phosphorus Transport and in 1α,25-Dihydroxycholecalciferol Synthesis

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Summary. A 50-year-old Latin American man with tumoral calcinosis presented with hyperphosphatemia (6.62 ± 1.04 SD mg/dl), elevated renal threshold phosphorus concentration (TmP) (7.3 mg/GFR), and 1,25-dihydroxyvitamin D [1,25-(OH)2D] (69 pg/ml) hypercalciuria (239 mg/day), and a high fractional intestinal calcium (Ca) absorption (0.74). Sodium cellulose phosphate therapy (20 g/day) lowered urinary Ca, and partially reduced serum phosphorus (P) and TmP to 5.91 ± 0.63 mg/dl and 6.2 mg/GFR, respectively. Serum 1,25-(OH)2D remained elevated at 58-64 pg/ml. Amphojel therapy (4 oz/day) decreased urinary P to 23 ± 21 mg/day and lowered serum P to 5.75 ± 0.36 mg/dl (P < 0.05). TmP increased to a value of 8.0 mg/GFR while serum 1,25-(OH)2D continued to remain elevated at 53 pg/ml.

This case illustrates the probable operation of dual abnormalities in tumoral calcinosis represented by augmented renal conservation of P and an elevation in the circulating concentration of 1,25-(OH)2D.

Key words: Ectopic calcification — 1,25-dihydroxyvitamin D — hyperphosphatemia — Bone — Renal tubule.

Introduction

Tumoral calcinosis is a rare metabolic disorder first described by Duret in 1899 [1]; this term was first used by Inclan et al. in 1943 [2]. The condition is characterized by deposits of amorphous calcium (Ca) phosphate, occurring as discrete “tumors,” and located adjacent to the major joints. Biochemically, tumoral calcinosis is often associated with hyperphosphatemia [3, 4], in the face of normal serum calcium and renal function.

The cause and pathogenesis of calcific deposits and the hyperphosphatemia associated with it remain obscure. Although tumoral calcinosis has been reported in patients given massive doses of vitamin D for arthritic diseases [5-7] and in patients with renal osteodystrophy receiving 1α-hydroxyvitamin D therapy [8], only in one study has the concentration of 1,25-dihydroxyvitamin D [1,25-(OH)2D] been measured. Prince et al. [9] found significantly elevated levels of 1,25-(OH)2D in seven siblings with hyperphosphatemia and tumoral calcinosis. The present study was undertaken to examine basic parameters of mineral metabolism, parathyroid function, and vitamin D status in a patient with tumoral calcinosis.

Experimental Subject

Case Report

A 50-year-old Latin American man was referred to us for evaluation of probable tumoral calcinosis. At the age of 7 years he had noticed a firm nodule on his left elbow. This nodule was surgically removed at age 28 years; it was said to contain calcium. At age 16 years, he was hospitalized for left hip pain, at which time radiologic examination disclosed the presence of nodular radiopaque masses adjacent to the femoro-iliac joint. At age 43 years, several nodules began to appear on the right elbow. They were nontender and freely mobile; a whitish material could sometimes be expressed by squeezing them.

The patient had no family history of similar ectopic calcifications or bone disease. The physical examination was essentially negative except for nodular deposits over the right elbow and over the hip. Radiological examination disclosed diffuse,
nodular "calcification" in the soft tissue over the lateral aspect of the left ischium and greater trochanter of the right femur and in the right elbow. One of the nodules on the right elbow was biopsied. This histological picture was compatible with the diagnosis of tumoral calcinosis [10]. The mineral constituent was found to be amorphous calcium phosphate. Initial laboratory evaluation disclosed serum phosphorus (P) of 6.4 mg/dl, serum Ca 9.9 mg/dl, creatinine (Cr) 1.0 mg/dl, albumin 4.4 g/dl, total protein 6.8 g/dl, alkaline phosphatase 65 IU, serum magnesium 2.2 mg/dl, plasma (fasting) glucose 88 mg/dl; normal serum sodium, potassium, chloride, carbon dioxide, lactic dehydrogenase, glutamic-oxaloacetic transaminase, and bilirubin; normal blood hematocrit; and normal serum T3 uptake, T4 and cholesterol. Bone density in the distal third of the radius by 125I-photon absorptiometry was normal at 0.753 g/cm² [11].

Sodium Cellulose Phosphate Trial. After the control study, the patient was begun on sodium cellulose phosphate (SCP, 20 g/day in four divided doses orally with meals) for 12 days, while he was maintained on the same dietary regimen. This procedure was undertaken to determine whether the inhibition of intestinal Ca absorption produced by SCP treatment would stimulate endogenous parathyroid function and modify the renal handling of P [16]. Tests performed during this period included: fasting serum for Ca, P, and Cr every 2 days; daily urinary Ca and P; and serum for iPTH, 1,25-(OH)₂D, 25-OHD, and 24,25-(OH)₂D, TmP, and urinary cyclic AMP, on day 12 of SCP treatment. The patient was then discharged and continued to take the sodium cellulose phosphate (15 g/day in three divided doses) as an outpatient for 12 months. At 6 and 12 months of SCP therapy, some of the above studies were repeated.

Study Protocol

The following study was conducted at the General Clinical Research Center after an informed written consent was obtained. The patient was placed on a metabolic diet with a daily composition of 400 mg Ca, 800 mg P and 100 mEq sodium. (This diet approximated his usual intake at home.) Total fluid intake was 3000 ml daily.

During the first 5 days, the following tests were obtained. Serum was obtained after an overnight fast and 1 h bed rest for growth hormone. Fractional (intestinal) Ca absorption was measured following an oral administration of 1 μCi ⁴⁷Ca in a 100 mg Ca carrier, as previously described [12, 13]. Heparinized blood containing a tracer amount of ³²P-pyrophosphate was obtained; pyrophosphate content was kindly determined by Dr. McCarty (Department of Medicine, University of Chicago, Pritzker School of Medicine, Chicago, Ill.) [14]. A fasting urine sample was obtained from 6-8 a.m., and serum obtained at 7 a.m. From the measured values of P and Cr, the renal threshold phosphorus concentration (TmP) was calculated [15].

Control Study. During Days 6-17 of the metabolic regimen lasting 12 days, urine was collected daily in 24-h pools and analyzed separately for Ca, P, Cr, and cyclic AMP. On day 7, venous blood was obtained in the fasting state for immunoreactive parathyroid hormone (iPTH), 1α,25-dihydroxyvitamin D [1,25-(OH)₂D], 25-hydroxyvitamin D (25-OHD), and 24,25-dihydroxyvitamin D [24,25-(OH)₂D]. During this control period, fasting venous blood was also obtained every 2 days for Ca and P.

Trial with Oral P-binding Agent

After 1 year of SCP therapy, the treatment was replaced by phosphorus-binding antacid (Amphojel) (4 oz/day orally, in 4 divided doses). After 12 months of Amphojel therapy, he was readmitted to the General Clinical Research Center, and reevaluated under the same metabolic dietary regimen, while receiving the same dose of the antacid. After 3 days of stabilization, a study period of 9 days was obtained, during which the following tests were performed: serum Ca, P, and Cr every 3 days; daily urinary Ca, P, Cr, and cyclic AMP; on the last day, serum iPTH, 1,25-(OH)₂D, 25-OHD, and 24,25-(OH)₂D, TmP, and urinary cyclic AMP, on day 12 of SCP treatment.

Following discharge, he was treated with SCP (15 g/day) and Amphojel (4 oz/day) for 12 months.

Analytical Procedures

Ca was determined by atomic absorption spectrophotometry, and P was measured by the method of Fiske and Subbarow [17]. Cr was measured in an Auto Analyzer (Technicon Instruments Corp., Tarrytown, NY). Urinary cyclic AMP (cAMP) was analyzed by the competitive protein-binding assay of Gilman [18]. Assay of sera for iPTH was performed as previously described [19] except that it was modified to use chicken 9 antisera (Immuno Nuclear Corp., Stillwater, Mn.), which is specific for the COOH-terminus of the PTH molecule. This antisera provides detectable values in 80% of normal subjects, high or inappropriately high values with respect to serum Ca in 95% of patients with primary