

CLINICAL CASE SEMINAR

Regression of Skeletal Manifestations of Hyperparathyroidism with Oral Vitamin D

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Context: Parathyroidectomy is the only effective therapy for osteitis fibrosa cystica in hyperparathyroidism.

Objective: The objective of this study was to describe the changes of skeletal and nonskeletal manifestations in a patient with hyperparathyroidism and renal failure after oral vitamin D therapy.

Design: This was a descriptive case report.

Setting: The patient was followed up in a referral center.

Patient: A 55-yr-old male patient with moderate renal failure was referred for expansile lytic lesions affecting several ribs and the spinous process of T12. His creatinine was 1.8 mg/dl; calcium, 8.9 mg/dl; PTH, 666 pg/ml; and 1,25 dihydroxy-vitamin D, 27 pg/ml. Bone mineral density (BMD) Z-scores by dual-energy x-ray absorptiometry were -4.1 at the spine, -1.7 at the hip, and -4.3 at the forearm.

Main Outcome Measures: The main outcome measures were the skeletal manifestations of hyperparathyroidism.

Results: At 10 months of therapy, calcium level was 10 mg/d, PTH level declined to 71 pg/ml, and BMD increased by 12% at the spine and 18% at the hip. Computerized tomography (CT) cuts revealed marked regression in the lytic lesions. At 2 yr, BMD increased by an additional 6% at the spine, and there were no further changes in the lytic lesions by CT. The vitamin D receptor genotype using the restriction enzymes *Bsm1*, *Taq1*, and *Apa1* was Bb, tt, and AA.

Conclusions: We showed regression of severe skeletal abnormalities of hyperparathyroidism documented by serial CT images in response to oral vitamin D therapy. It is possible that the vitamin D receptor genotype of the patient modulated this response. (*J Clin Endocrinol Metab* 91: 2480–2483, 2006)

OVER THE LAST four decades, the phenotype of primary hyperparathyroidism has substantially changed. Because of the common use of multichannel biochemical screening, clinically evident skeletal involvement has become very uncommon nowadays (1). Whereas many patients with modern primary hyperparathyroidism have decrements in bone mineral density (BMD), abnormal radiological findings are quite rare (2) and are more common in secondary hyperparathyroidism of chronic kidney disease (3). Parathyroidectomy results in reversal of bone loss (4) and is the only effective therapy for osteitis fibrosa cystica in primary hyperparathyroidism (5).

We present a case of severe hyperparathyroidism with severe bone loss and profound skeletal changes of the ribs and spine that regressed dramatically after oral therapy with vitamin D.

Patient and Methods

Serum creatinine, calcium, phosphorus, and alkaline phosphatase were measured with standard colorimetric methods using the Hitachi

912 analyzer (Mannheim, Germany). Serum PTH was measured by ELSA-PTH immunoradiometric assay (CisBio International, Gif-Sur-Yvette, Cedex, France), with a normal range of 10–76 pg/ml and intra- and interassay coefficient of variation (CV) less than 10%. Serum 25-hydroxy vitamin D (25 OHD) was measured by a competitive protein-binding assay with inter- and intraassay CV less than 13% (Diasorin Incstar; Diasorin, Saluggia, Italy). Serum 1,25 dihydroxy-vitamin D [$1,25(\text{OH})_2\text{D}$] was measured by RIA using the IDS (Immunodiagnostic System Limited, Boldon, UK). The reference range reported in the kit insert was 20–46 pg/ml.

Areal BMD (grams per square centimeter) of the anteroposterior lumbar spine (L1–L4), left femur (total hip, femoral neck, and trochanter), and left 1/3 radius were measured by dual-energy x-ray absorptiometry, using a Hologic 4500A device (Hologic, Bedford, MA). Precision estimates (mean \pm sd) for densitometry measurements at our center, expressed as CV (percent) based on serial duplicates for the period overlapping the observation period for this patient were as follows: $0.80 \pm 0.6\%$ at the lumbar spine ($n = 567$), $0.81 \pm 0.7\%$ at the total hip ($n = 571$), and $0.92 \pm 0.7\%$ at the forearm ($n = 569$).

DNA was extracted from whole blood, and polymorphisms in the vitamin D receptor (VDR) gene were examined by PCR followed by digestion with the restriction enzymes *Bsm1*, *Taq1*, and *Apa1* (6).

Verbal consent was obtained from the patient for VDR genotyping.

Case report

A 55 yr-old male was referred to our clinic on July 2002 for evaluation for multiple lytic lesions of the ribs and spinal process of the dorsal vertebrae. The patient fell down and fractured three ribs a few years before presentation and since then had exacerbation of the bone pain in the rib cage area every few weeks. Chest x-ray showed a suspected lung mass that was later reassessed and read as a large bony lesion of the rib, and a computerized tomography (CT) scan of the chest revealed mul-

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Abbreviations: BMD, Bone mineral density; CT, computerized tomography; CV, coefficient of variation; $1,25(\text{OH})_2\text{D}$, 1,25 dihydroxy-vitamin D; 25 OHD, 25-hydroxy vitamin D; VDR, vitamin D receptor.

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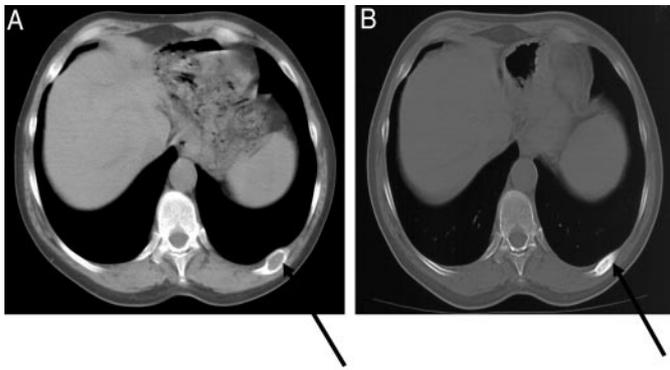


FIG. 1. A, Lytic expansile lesion of the posterior arch of the left 11th rib. B, Decrease in the size of the lesion with healing by sclerosis at 10 months of therapy.

multiple lytic expansile lesions involving the ribs and the spinal process; the largest lesion was in the anterior arch of the left 11th rib and in retrospect deemed responsible for the impression of a left upper lobe mass on the original chest x-ray. Upon questioning, the patient recalled a history of forearm fracture and pelvic fracture several years before his presentation but denied any height loss. The differential diagnosis included multiple myeloma or hyperparathyroidism and Brown tumors (Figs. 1A, 2A, and 3A).

The patient carries a thalassemia trait and has been hypertensive with moderate renal failure since 1994. At that time, his creatinine was 2.0 mg/dl, and evaluation of the renal failure with an ultrasound revealed an atrophic right kidney; a kidney biopsy showed moderate arterio- and arteriolonephrosclerosis.

When he presented to our clinic, there was no bone mass or tenderness on physical examination of the anterior or posterior ribs or thoracolumbar spine on palpation. He was on Tritace (ramipril), Zyloric (allopurinol), and Esidrex (hydrochlorothiazide). Laboratory studies available at that time included blood urea nitrogen 74 mg/dl and serum creatinine 1.8 mg/dl. His calculated creatinine clearance based on 24-h urine collection was 32 ml/min. Serum calcium was 8.9 mg/dl with normal serum albumin level, serum phosphorus 2.8 mg/dl, and alkaline phosphatase 317 IU/liter. Urinary calcium excretion was 20 mg/d. Intact PTH was 666 pg/ml and serum 1,25 (OH) vitamin D was 27 pg/ml. Additional laboratory results included a serum 25 OHD of 25 ng/ml (on 800 IU/d vitamin D), normal serum and urine protein electrophoresis, serum testosterone levels, TSH, serum glutamic-oxaloacetic transaminase, and serum glutamate pyruvate transaminase. Antiendomysial antibodies were negative. Ultrasound of kidneys showed a small right kidney with presence of simple cortical cysts in both kidneys. BMD Z-score was -4.1 at the lumbar spine, -1.7 at the total hip, -1.0 at the femoral neck, and -4.3 at the 1/3 radius. Instant vertebral morphometric assessment by dual-energy x-ray absorptiometry from T5 to L5 revealed no evidence of vertebral compression fracture.

The working diagnosis was severe secondary hyperparathyroidism with severe bone loss and osteitis fibrosa cystica in a 55-yr-old male patient with stage 3 chronic kidney disease. The patient was originally started on alfacalcidol 0.25 $\mu\text{g}/\text{d}$ along with calcium carbonate 1000 mg/d and 800 IU of vitamin D₃. The alfacalcidol was subsequently increased to 0.5 μg daily. Within 4 months of therapy, his serum calcium was 9.5 mg/dl, serum phosphorus was 2.8 mg/dl, and his PTH level had dropped to 389 pg/ml. The dose of alfacalcidol was again increased to 1 $\mu\text{g}/\text{d}$, which resulted in further decline in the PTH level to 125 pg/ml at 7 months of therapy. Ten months after starting vitamin D therapy, BMD had increased by 12% at the spine and 18% at the hip with normalization of Z-score at that site, but there were no changes at the forearm. CT scan of the chest revealed marked regression in the lytic lesions in the ribs and dorsal vertebrae with a decrease in the size of all lesions and filling in of bone by sclerosis at 10 months of therapy (Figs. 1B, 2B, and 3B). At that time, weekly alendronate was added at a modified dose of 35 mg/wk (half-tablet of the 70-mg preparation) due to the renal failure. Because the calcium level had increased to 10 mg/dl, the dose of alfacalcidol was cut down to 0.5 $\mu\text{g}/\text{d}$, which resulted in a rapid increase of the PTH level to 203 pg/ml after 3 months of decreasing

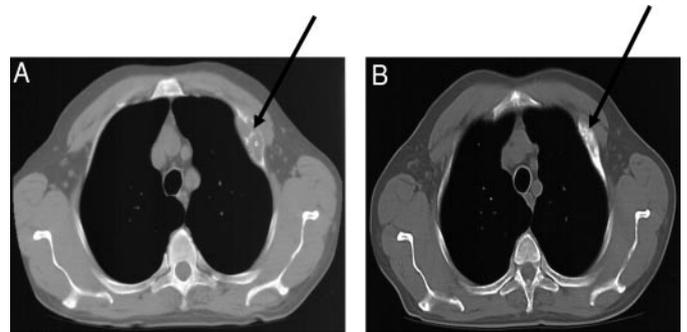


FIG. 2. A, Lytic expansile lesion of the anterior arch of the second rib with cortical thinning and minimal destruction and sclerotic septum. B, Significant decrease in the size with sclerosis at 10 months of therapy.

the dose. However, it came down to 46 pg/ml when the high dose of 1 $\mu\text{g}/\text{d}$ alfacalcidol was resumed. After 2 to 3 yr of starting therapy, his serum calcium levels were for the most above 10 mg/dl, and his PTH level fluctuated between 64 and 93 pg/ml. Details of changes in his serum chemistries and calciotropic hormones are shown in Table 1. After 2 yr of therapy his BMD had further increased by 6% at the spine and remained stable at the hip and forearm, and there were no further changes in the lytic lesions by CT. No further improvement in BMD was seen at the third year.

The VDR genotype identified by DNA extraction was Bb, tt, and AA, respectively.

Results and Discussion

This case illustrates a marked sustained improvement of hyperparathyroidism, with substantial decrements in PTH levels, paralleled with regression of the size and increased sclerosis of the expansile bony lesions carefully documented by serial CT scans after treatment with both oral cholecalciferol and alfacalcidol.

Reports of patients with primary hyperparathyroidism and osteitis fibrosa cystica revealed substantial increments in BMD at the spine, hip, and forearm by 100–550% after parathyroidectomy (5, 7). Kulak *et al.* showed normalization of T scores in two young patients with severe primary hyperparathyroidism (5). Our patient had substantial increment in BMD at the spine and the hip at 1 and 2 yr of therapy, but there was no response at the forearm. The absence of response at the forearm in this case as opposed to the increment observed in the two other studies may be in part explained by the substantially higher PTH levels in the reported cases

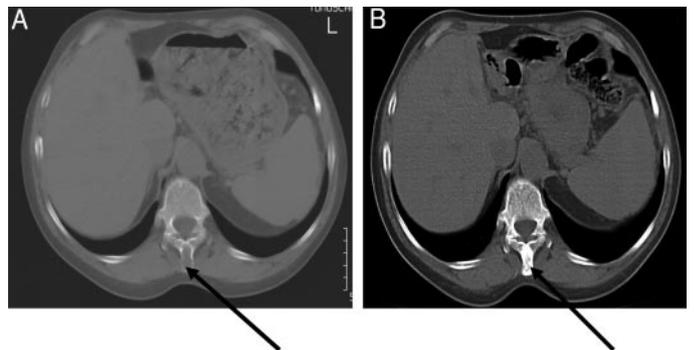


FIG. 3. A, Lytic slightly expansile lesion with cortical thinning involving the spinal process of T12 vertebrae. B, Healing of the lesion by sclerosis at 10 months of therapy.

TABLE 1. Characteristics of the patient at baseline and during treatment

	Baseline	4 months	7 months	10 months	13 months	16 months	24 months	33 months	38 months
Serum biochemistries [normal values]									
Creatinine (mg/dl) [0.6–1.2 mg/dl]	1.8	1.7	1.7	1.9	NA	NA	1.6	1.7	1.7
Calcium (mg/dl) [8.5–10.5 mg/dl]	8.9	9.5	9.5	10	9.6	10.5	10.4	10.5	10.2
Phosphorus (mg/dl) [2.9–5.2 mg/dl]	2.8	2.8	2.5	2.9	2.6	4	3.6	3.1	3.0
Alkaline phosphatase (IU/liter) [35–120 IU/liter]	317				103	97	84	68	
Serum PTH (pg/ml) [8–76 pg/ml]	666	389	125	71	203	46	35	64	74
Serum 1,25(OH) ₂ D (pg/ml) [20–46 pg/ml]	27	27	46	13	62	NA	27	NA	38
Serum 25 OHD (ng/ml)	25 ^a			24			31	26.9	
BMD									
L1–L4 (g/cm ²)	0.590			0.712			0.755	0.748	0.758
Total hip (g/cm ²)	0.721			0.867			0.884	0.895	0.895
Forearm (g/cm ²)	0.553			0.541			0.552	0.578	0.549
L1–L4 Z-score	–4.1			–2.9			–2.5	–2.5	–2.4
Total hip Z-score	–1.7			–0.7			–0.6	–0.5	–0.5
Forearm Z-score	–4.3			–4.5			–4.3	–3.7	–4.3

^a Obtained after 12 wk of supplementation with cholecalciferol 800 IU/d.

(5) and the fact that they had no renal failure (5, 7). The proposed mechanism for the increase in bone mass is a reduction in the remodeling space (5), an improvement previously noted to occur at sites rich with high turnover bone. However, the sustained increase in BMD at the spine in the second year and the absence of response at the forearm suggest an additional mechanism of the bone anabolism when correcting the high PTH levels.

A few studies documented the postoperative course of the radiological aspect of osteitis fibrosa cystica and none had used CT images (7, 8). Agarwal *et al.* (7) showed that after parathyroidectomy, Brown tumors regressed only partially, as assessed by plain x-ray films, in six of 27 patients with primary hyperparathyroidism who had such deformities. Calcitriol is the principal regulator of PTH cell proliferation and secretion. Lumb and Stanbury (9) showed healing of the rickets and osteitis fibrosa cystica with vitamin D therapy in a 14-yr-old girl with non-azotemic rickets, and some reports have shown that iv alfacalcidol or calcitriol is effective treatment for secondary hyperparathyroidism in subjects on dialysis (10–13). These agents reduce PTH secretion and parathyroid cell hyperplasia, and in some cases they resulted in regression of Brown tumors without surgical treatment (10, 11). The most substantial increments in BMD and the regression in the lytic lesions occurred within the first year of therapy coinciding with the almost normalization in intact PTH levels. Mourad *et al.* (11) showed improvement of severe hyperparathyroidism and partial regression of osteitis fibrosa cystica with Brown tumor of the mandible after iv alfacalcidol in a patient with end-stage renal disease and a PTH level above 1000 pg/ml. This management was limited by the vitamin D-induced hypercalcemia because of the high dose needed and the elevation in calcium phosphorus product (10).

In subjects with mild to moderate renal failure, PTH levels ranged between 17 and 383 pg/ml (14). Our patient has had moderate impairment in his kidney function consistent with stage 3 kidney disease (15) that was stable over 10 yr. His PTH level exceeded the expected range, and his skeletal manifestations were out of proportion to the degree of renal failure and elevation of alkaline phosphatase level. He had no symptoms of malabsorption and his antiendomysial an-

tibodies were negative. The serum calcium level and the very low urine calcium at presentation suggested that the patient had secondary hyperparathyroidism. His serum 25 OHD was normal, but the patient might have been vitamin D deficient and the first reported normal 25 OHD value probably reflected recent vitamin D supplementation. However, the consistently high serum calcium levels (above 10 mg/dl) after 1 yr of treatment with calcium and vitamin D and the impaired suppression of PTH levels as serum calcium increased suggest a possible underlying primary hyperparathyroidism.

Distinguishing between primary and secondary hyperparathyroidism in patients with renal disease has always been a diagnostic problem (16). Dent (16) suggested a vitamin D challenge test to unmask primary hyperparathyroidism in patients with normal serum calcium levels and severe hyperparathyroidism and bone disease, and patients become hypercalcemic only when vitamin D is replete as may have been the case here.

The VDR plays a role in regulating calcium metabolism through binding and nuclear translocation of 1,25(OH)₂ D, thus modulating bone resorption and increasing intestinal calcium absorption. Some polymorphic alleles of VDR have been implicated in the development of hyperparathyroidism and determination of serum PTH levels (17–19). Carling *et al.* (17) showed dominance of baT haplotype in patients with primary hyperparathyroidism but did not find a significant association between genotypes and intact PTH level. Yokohama *et al.* (18) found that, in Japanese patients with end-stage renal disease, the intact PTH level in the aa group was about twice as high as those in the AA and Aa groups, but there was no difference between the Bb and bb groups. Vigo Gago *et al.* (19) showed that patients with FF genotype of the FokI polymorphism of the VDR gene have the highest levels of PTH. Our patient did not have any of the above-reported genotypes that were associated with primary hyperparathyroidism or with higher PTH levels in renal failure. The follow-up question that poses itself is whether the dramatic skeletal response to calcium and vitamin D could be related to VDR genotypes. The data on such question are scarce and contradictory (20–22). One *in vitro* study showed that VDR polymorphisms are not involved in the response to calcitriol

of parathyroid tissue cultured from subjects with secondary hyperparathyroidism (20). Conversely, Carling *et al.* (22) found that, when dispersed cells of parathyroid adenomas extracted from 62 subjects with primary hyperparathyroidism were exposed to external calcium, cells extracted from homozygous subjects for the VDR alleles a, b, and T showed lesser suppression of PTH release, whereas maximal PTH suppression showed higher values for cells extracted from subjects with the AA genotype (22). Marco *et al.* (21) showed that in 17 patients with secondary hyperparathyroidism, subjects with BB genotype had significant suppression of PTH level at 48 and 72 h after a single bolus of calcitriol, whereas bb subjects did not. In our patient, the marked and dramatic response in PTH level to oral calcium and vitamin D therapy, the rise in PTH level when the alfacalcidol dose was decreased, and the dramatic response to increasing the dose again are all consistent with the reported response in PTH levels to calcium and calcitriol by specific VDR genotype (21, 22).

More than 20 yr ago, Stanbury (23) suggested that 25 OHD was able to heal uremic osteomalacia and that 1,25(OH)₂D was not essential for that therapeutic effect. Because the dose of alfacalcidol was not very high and the highest value of 1,25(OH)₂D achieved was 62 pg/ml, it is possible that vitamin D, the parent compound rather than alfacalcidol, played the major role in the reduction in PTH levels and the regression of bone lesions.

In conclusion, PTH levels decreased and skeletal manifestations markedly improved as carefully documented by CT scan with oral vitamin D therapy in a 55-yr-old male patient with severe hyperparathyroidism. The VDR genotype of the patient may have modulated his marked response to oral vitamin D therapy.

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Conflict of interest: Authors have nothing to declare.

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