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Pitfalls in Parathyroid Evaluation in Patients with Calcium Urolithiasis*

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Summary. Primary hyperparathyroidism is a major cause of calcium urolithiasis and is easily recognised when it is classically manifested. However, subtle presentations of primary hyperparathyroidism may cause confusion with other causes of calcium stone disease or cause diagnostic difficulty. Several pitfalls of parathyroid evaluation and treatment are illustrated by four cases of calcium urolithiasis. Cases 1 and 2 represent ineffective or useless parathyroid surgery rendered for renal hypercalciuria and absorptive hypercalciuria, respectively. Cases 3 and 4 had mild or intermittent hypercalcaemia. The correct diagnosis of primary hyperparathyroidism was made in Case 3 by parathyroid venous sampling and bone densitometry. In Case 4, the thiazide provocative test was used to establish the diagnosis of primary hyperparathyroidism.

Key words: Nephrolithiasis, Hyperparathyroidism.

INTRODUCTION

Primary hyperparathyroidism is recognised as a major cause of calcium (Ca) urolithiasis (3, 9, 17, 28, 33). Successful surgical removal of the abnormal parathyroid tissue usually results in alleviation of the Ca stone disease (15, 18). When primary hyperparathyroidism is classically expressed, the diagnosis usually presents no problems. However, subtle manifestations of this disease may cause confusion with other causes of Ca urolithiasis (6, 22). This confusion has led, on occasion, to the recommendation of parathyroid surgical exploration in renal (7) and absorptive hypercalciurias (19, 24), the two principal variants of "idiopathic" hypercalciuria. Further difficulty may be encountered in defining indications for parathyroid surgery in patients with primary hyperparathyroidism, in whom serum calcium is only slightly or intermittently elevated.

Such pitfalls, which may arise in the evaluation and treatment of parathyroid disease, are illustrated by the following four cases of Ca stone disease. Cases 1 and 2 are patients with renal hypercalciuria and absorptive hypercalciuria, respectively, in whom parathyroidectomy was done without benefit. Cases 3 and 4 had primary hyperparathyroidism with a mild or intermittent hypercalcemia. Case 3, with initially unsuccessful parathyroid venous sampling and bone densitometry. In Case 4, the diagnosis was facilitated by thiazide provocation test.

CASE REPORTS

Case 1. A thirty-nine year old white women who spontaneously passed over 200 stones from 1959 to 1973, requiring 50 admissions to hospital. Analysis of the stones revealed the presence of both apatite (Ca phosphate) and Ca oxalate. Initial evaluation in August of 1974 revealed a blood pressure of 120/76, pulse of 76, and a normal physical examination. Serum Ca and phosphorus (P) were normal at 9.5 mg/dl and 3.6 mg/dl, respectively. While maintained on a constant diet containing 400 mg Ca and 100 meq sodium daily, she had hypercalciuria of 260-288 mg/day (normal <200 mg/day),

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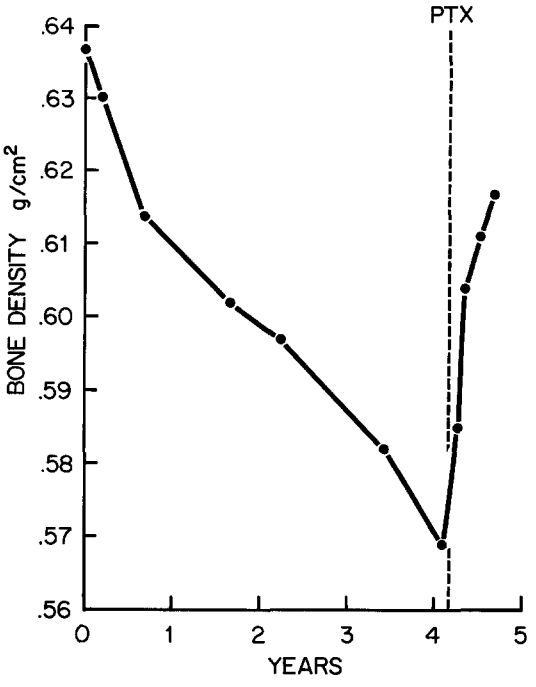

Fig. 1. Effect of parathyroidectomy (PTX) on bone density in Case 3 with primary hyperparathyroidism

and an elevated mean urinary cyclic AMP excretion of 5.60 μmols/g creatinine (normal < 5.40 μmols/g creatinine) (24). In addition, she had a high fasting urinary Ca of 0.16 mg/mg urinary creatinine (normal < 0.11 mg/mg) (23). The abdominal radiograph disclosed the presence of bilateral radiopaque renal calculi. These findings indicated she had an impaired renal tubular reabsorption of Ca. It was felt she suffered from renal hypercalciuria with secondary hyperparathyroidism (7, 23).

Unfortunately, she failed to adhere to the recommended medical therapy and was lost to follow-up. In August 1975, she was hospitalised for renal colic at another hospital. She reportedly had a high serum immunoreactive PTH (iPTH) and normal serum Ca. The patient was felt to be suffering from normocalcaemic primary hyperparathyroidism (6, 13, 16, 34) and was subjected to neck exploration. During surgery, all four parathyroid glands were found to be slightly enlarged. Two glands were resected in toto; the remaining glands were biopsied. Parathyroid hyperplasia was found in all glands.

Postoperatively, the patient remained normocalcaemic, hypercalciuric and continued to form new Ca stones. She was re-evaluated during August 1976, at which time our initial impression of renal hypercalciuria was confirmed. Serum Ca and P were normal at 9.2 and 3.1, respectively. Both 24-hour and fasting urinary Ca were elevated at 389 mg/day and at 0.22 mg/mg creatinine, respectively. On treatment with hydrochlorothiazide (50 mg twice/day), her urinary Ca decreased to normal, and she has formed fewer stones.

Case 2. A fifty-seven-year-old white man who first passed a Ca-containing stone at the age of 22. He remained stone-free for 11 years, then became severely afflicted with recurrent passage of Ca stones. From 1958 to 1973, he spontaneously passed 12 stones and underwent 6 uretero- or nephrolithotomies for obstruction with stones. In 1964, he was found to be hypercalciuric. Despite persistently normal serum Ca determinations, the patient was subjected to a neck exploration in 1964 on the basis of a reduced renal tubular reabsorption of P. During the parathyroid exploration, four normal-sized parathyroid glands were identified. No parathyroid tissue was removed. The surgical procedure did not alleviate his Ca stone disease.

In July 1973, evaluation disclosed normal serum Ca and P of 9.2 mg/dl and 3.4 mg/dl, respectively. Urinary Ca was high at 316-368 mg/day. Serum iPTH[1] was undetectable and urinary cyclic AMP was low normal at 2.21-2.76 μmols/g creatinine (24). His fractional intestinal Ca absorption was elevated at 0.78 (normal < 0.61) (24). A diagnosis of absorptive hypercalciuria was made and the patient was begun on sodium cellulose phosphate therapy (21). After 3 months of treatment, his urinary Ca had decreased to 132 mg/day. He remains on this therapy and has had no new stone formation after 42 months of treatment.

Case 3. A seventy-two-year-old black woman, underwent a left total nephrectomy in 1971 for a staghorn calculus and a non-functioning kidney.

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[1] Serum immunoreactive PTH was assayed according to the modified procedure of C. Arnaud et al. Radioimmunoassay of human parathyroid hormone in serum. Journal of Clinical Investigation 50, 21 (1971). Antiserum (batch AS 211/32, Burroughs Reagents Ltd., England) measured both the COOH- and the NH_2-terminus of the PTH molecule. Bovine PTH (Inolex Biomedical, Glenwood, Illinois), iodinated with ^{131}I sodium (New England Nuclear, Boston, Mass.), was used as a tracer. Standard curves were constructed using human PTH obtained from human parathyroid tissue culture (generous gift of Dr. B. Roos). All serum samples were assayed in duplicate. In our hands, this assay provided detectable values in 65% of normal subjects, high or inappropriately high values in 60-70% of patients with primary hyperparathyroidism, and increased serum concentrations > 95% of patients with renal osteodystrophy

During that hospitalization, she was found to be hypercalcaemic (serum Ca 11.0-11.5 mg/dl) and hypophosphataemic (2.2 mg/dl). Normal serum Ca was not restored following administration of prednisone. In 1971, she underwent parathyroid exploration. The only parathyroid gland identified at surgery was the right superior gland; it was removed and found to be histologically normal. The left lobe of her thyroid gland was resected during this procedure and a small, normal parathyroid gland was found embedded in the thyroid tissue.

Following her surgery, she was intermittently hypercalcaemic. In August 1973, she was re-evaluated in the General Clinical Research Center. Physical examination revealed a blood pressure of 160/100, pulse of 64/min, respiratory rate of 14/min and temperature of 98.6 F. She had a slight cardiomegaly with a Grade ii/vi systolic murmur at apex. Serum Ca was high (10.9-11.5 mg/dl) and serum P low (2.4 mg/dl). Urinary Ca was slightly increased (201-250 mg/day). Urinary cyclic AMP was high (5.30-8.15 μmols/g creatinine) (24) and did not decrease following an oral Ca load. Serum iPTH was inappropriately elevated at 26 μl eq/ml. The diagnosis of persistent primary hyperparathyroidism was made.

It was elected to follow the patient without further surgery, since she was asymptomatic and as she was reluctant to undergo further evaluation. From August 1973 to February 1977, serum Ca fluctuated from 9.8-11.5 mg/dl. However, bone density (in the distal third of the radius by ^{125}I-photon absorptiometry) progressively declined (Fig. 1) (5, 24).

In November 1976, the patient developed an obstructive right ureteric calculus which required surgical removal. Because of her recurrent stone disease, she was persuaded to undergo venous sampling of her neck veins via catheterisation for sequential measurements of PTH, in order to pre-operatively localise abnormal parathyroid tissue (27, 30). A 3-fold increase in iPTH was noted at the level of the right inferior thyroid vein. In February 1977, an 800 mg parathyroid adenoma was found within the right thyroid gland and resected. Another gland of normal size was identified at surgery and left intact.

Following surgery, the patient was transiently hypocalcaemic. The patient has subsequently maintained normal serum and urinary Ca. Serum immunoreactive PTH and urinary cyclic AMP became normal at 15 μ eq/ml and 2.57 μmols/g creatinine, respectively. Her bone density increased by 8% from pre-operative values (Fig. 1).

Case 4. A sixty-seven-year-old retired man, developed a staghorn calculus of his left kidney in September 1974. Following surgical removal of the calculus, he required right ureterolithotomy in December 1974. He denied a history of ulcers, bone disease, or an infection of the urinary tract. In July 1975, he was evaluated at the General Clinical Research Center. Serum Ca ranged from 9.7-11.4 mg/dl, and serum P from 2.2-3.1 mg/dl. Urinary Ca was normal (107- 151 mg/day). Serum iPTH was slightly high at 45 μ eq/ml (normal < 40). Urinary cyclic AMP was normal (2.30-4.06 μmols/g creatinine). Because of these uncertain results, he was reevaluated in September 1975. The results of this evaluation were essentially normal. Serum Ca ranged from 9.8-10.3 mg/dl, and urinary Ca 143-169 mg/day. Serum iPTH was undetectable and urinary cyclic AMP was normal (2.96-4.88 μmols/g creatinine). Fasting urinary Ca was normal at 0.1 mg/mg creatinine. He was begun on thiazide (hydrochlorothiazide 50 mg twice/day). Frank hypercalcaemia (10.8-11.8 mg/dl) and hypophosphataemia (2.1-2.4 mg/dl) developed. Serum immunoreactive PTH was inappropriately high for the degree of serum Ca at 32 μ eq/ml. In February 1977, the patient underwent the successful removal of a single parathyroid adenoma weighing 600 mg. Three normal parathyroid glands were identified. Postoperatively, the patient has no identifiable abnormality of his Ca or parathyroid status.

DISCUSSION

Primary hyperparathyroidism is recognised as one of the major causes for Ca urolithiasis (3). Unfortunately, many problems may arise in the evaluation of parathyroid status in patients with Ca stones.

The four cases presented here with Ca urolithiasis and normocalcaemia or intermittent hypercalcaemia, emphasise the need for an accurate diagnosis of primary hyperparathyroidism before parathyroid surgery is undertaken. Cases 1 and 2 represent patients with renal hypercalciuria, and absorptive hypercalciuria, respectively, in whom useless parathyroid exploration was performed for mistaken diagnoses. In Cases 3 and 4 with "atypical" primary hyperparathyroidism, the diagnosis was facilitated by the use of parathyroid venous drainage, bone densitometry and thiazide provocation.

In Cases 1 and 2, the diagnosis of renal and absorptive hypercalciurias was confused with that of primary hyperparathyroidism. These two conditions probably represent the two major variants of idiopathic hypercalciuria, in which the excessive renal excretion of Ca is believed to result from an impairment in the renal tubular reabsorption (renal leak) or (7, 24) an intestinal hyperabsorption of Ca.

The characteristic features of renal hypercalciuria (7, 23, 24) which Case 1 satisfied, are: recurrent Ca urolithiasis, hypercalciuria, secondary hyperparathyroidism, elevated fasting urinary Ca and normocalcaemia. The hyperparathyroidism is presumed to be secondary, since normal para-

thyroid function may be restored by an oral Ca load (23) or by the correction of renal leak of Ca by thiazide (10). This condition should be distinguished from normocalcaemic primary hyperparathyroidism, in which some degree of parathyroid autonomy is believed to be present (13, 16, 34). Although the exact underlying pathophysiologic mechanisms have not been clarified, normocalcaemic primary hyperparathyroidism may represent a mild form of primary hyperparathyroidism. While serum Ca is usually within the normal range, it may be high normal or intermittently elevated (16). Following parathyroidectomy, a decrease in serum Ca may be found though occurring within the normal range.

It is critical that renal hypercalciuria with secondary hyperparathyroidism is clearly differentiated from normocalcaemic primary hyperparathyroidism. Parathyroidectomy is contraindicated in renal hypercalciuria. The recurrence of biochemical abnormalities and stone formation would be expected in renal hypercalciuria, as illustrated by this case. The high recurrence rate of urolithiasis and frequent demonstration of parathyroid hyperplasia in patients with normocalcaemia and hyperparathyroidism (6) suggest certain patients who underwent the parathyroid surgery for normocalcaemic primary hyperparathyroidism, may have suffered from renal hypercalciuria.

The need for avoiding parathyroidectomy in renal hypercalciuria becomes more acute, since an effective medical therapy for this condition may be available. As noted before, thiazide may restore normal urinary Ca and parathyroid function in renal hypercalciuria, without causing hypercalcaemia (7). If intestinal Ca absorption is high, thiazide has been shown to reduce it toward normal (5). Moreover, this drug has been shown to inhibit new stone formation (8, 35).

The above response to thiazide in renal hypercalciuria is clearly different than that in primary hyperparathyroidism. In the latter condition, thiazide typically does not restore normal parathyroid function, and may cause or exaggerate the hypercalcaemia (4, 26). This thiazide provocation should be considered in patients in whom the diagnosis of primary hyperparathyroidism is suspected but uncertain. It may facilitate the diagnosis of primary hyperparathyroidism in patients with normocalcaemia or intermittent hypercalcaemia, as illustrated by Case 3.

Case 2 suffered from absorptive hypercalciuria since he had recurrent Ca nephrolithiasis, intestinal hyperabsorption of Ca, hypercalciuria and normal or suppressed parathyroid function (19, 23, 24). Some patients with this condition may present with hypophosphatemia and high renal P clearance. This indirect evidence of excessive parathyroid activity should not lead to the diagnosis of primary hyperparathyroidism as was done in this case. Parathyroid function, assessed by serum iPTH and urinary cyclic AMP, is normal or suppressed in absorptive hypercalciuria (24). The diagnosis of absorptive hypercalciuria is not usually difficult. This condition should be suspected in patients with Ca urolithiasis, if fasting urinary Ca is normal and if there is an exaggerated renal loss of Ca following an oral Ca load (23), even when the values of serum iPTH and urinary cyclic AMP are not known. The uselessness of parathyroid surgery is emphasised by the increasing evidence that recurrent nephrolithiasis of absorptive hypercalciuria may be effectively controlled medically with sodium cellulose phosphate (2, 20, 21), orthophosphate (1, 32), or thiazide (8, 35). This case, for example, responded favourably to oral sodium cellulose phosphate, a non-absorbable cation exchange resin which binds Ca and inhibits intestinal Ca absorption (2).

Cases 3 and 4 illustrate the problems in the evaluation and management of mild recurrent or intermittent primary hyperparathyroidism. Case 3 demanded an accurate assessment of parathyroid status, since she had lost one kidney from renal stones and had already undergone an unsuccessful parathyroid surgery. A successful study of parathyroid venous drainage (11, 27, 30) was performed to localise the abnormal parathyroid gland. The need for the reexploration surgically was indicated by the progressive decline in bone density. Bone mineral content must decrease by 25% before evidence of "dimineralisation" is detectable by conventional roentgenogram (14). Significant bone mineral loss may be detected prior to x-ray changes with the use of photon absorptiometry (10, 12, 24), particularly in post-menopausal women (25). Case 3 had normal bone density by ^{125}I-photon absorptiometry when initially seen. However, bone density decreased by 11% over 4 years. This dramatic loss of bone mineral content corroborated the adverse effects of hyperparathyroidism and emphasised the need for parathyroid surgery. Following parathyroidectomy, bone density increased by 8% over 5 months, a finding which supported the dependence on parathyroid status of changes in bone density.

Case 4 documents an intermittent form of primary hyperparathyroidism. Parathyroid function was clearly normal during part of his course. The diagnosis was facilitated when the patient developed persistent hypercalcaemia during thiazide therapy (4, 26).

In conclusion, pitfalls in the diagnosis and in the assessment of the need for parathyroid surgery may be minimized by a meticulous attention to the more subtle presentation of primary hyperparathyroidism and the proper recognition of diseases simulating this condition.

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