**Brief report**

# A renal stone patient with a "hesitant" hyperparathyroidism

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**Presentation of a clinical case**

A 50-year old man was referred to our outpatient clinic by the Conegliano Hospital Urological Department, where he had undergone right percutaneous pielolithotomy for an obstructing stone. Previously, he had had one calcium-oxalate stone which passed spontaneously. His personal and familial history was not significant. The patient was normotensive and had normal thyroid and renal functions. He was not taking any drug or nutritional supplement.
The diagnostic workout of the stone metabolic risk disclosed a very severe hypercalciuria (317 to 912 mg/day), occasionally associated with borderline hypercalcemia. Serum phosphate was in the normal range; other tests (citraturia, uricosuria, urine and blood pH, blood bicarbonate) were also normal. A low calcium diet and thiazide administration modified calciuria only moderately, but thiazides induced modest, non-transient hypercalcemia (11.4 mg/dL). Calciuria was high even after fasting. Secondary forms of neoplastic, granulomatous, and monoclonal disorders were ruled out, and primary hyperparathyroidism was suspected. The thiazides-induced hypercalcemia was suggestive of this condition. However, PTH levels were repeatedly normal (34 ng/L, and 47 ng/L concomitant with the thiazide-induced hypercalcemia), ionized calcium was in the normal range, and the parathyroid US and nuclear scans were both negative.
Although bone densitometry showed normal values, bone turnover was increased as evidenced by higher urine excretion of cross-links and hydroxy-proline. This finding, together with fasting hypercalciuria, suggested a renal form of hypercalciuria. The patient was then treated with the lowest dosage of hydrochlorothiazide (12.5 mg), which did not induce hypercalcemia; potassium citrate 6 g/day was also administered with a recommendation to increase water intake.
In the following year, no new stone formed. However, calciuria was again very high (>500 mg/day) and, for the first time, PTH too was abnormally elevated (127, 138 ng/L). Parathyroid US and nuclear scans were both negative. The hypothesis was advanced that hypercalciuria was primarily of renal (or bone) origin with secondary activation of the parathyroids. After a 2 week wash-out from thiazides, urine sodium excretion was still high (241 mmol/day); therefore, a short trial with a hyposodic diet was performed after which calciuria was significantly reduced, although it remained slightly elevated (310 mg/day). The patient was thereafter strongly recommended to follow a strict low sodium regimen together with hydrochlorothiazide (50 mg/day). A year later, PTH was decreased to normal values (59, 64 ng/L), and serum calcium (10.0 mg/dL) and calciuria (290 mg/day) were both in the normal range. No other stone had formed in the meantime.
This case is interesting in three aspects: 1) the way it fits in different classifications of hypercalciuria; 2) it shows a need to approach treatment by acting on different mechanisms; and 3) it suggests the possibility of reversing secondary hyperparathyroidism.
A number of classification types of hypercalciuria have been developed over time. Pak et al (1) classified hypercalciuria as absorptive, renal or resorptive. In view of this classification, the patient appeared to be affected by renal hypercalciuria during his initial evaluation. According to Bataille et al (2) who, essentially developing Pak's original classification (1), proposed six different patho-physiological types of hypercalciuria (absorptive tp. I, tp. II, tp. III, renal, fasting and dietary-calcium-dependent), our patient had a mixed form of renal and fasting hypercalciuria. Certainly, this case is atypical because it presents a number of conditions which are not distinctive of a single form of hypercalciuria. Fasting hypercalciuria with normal serum calcium and PTH seem to indicate severe absorptive hypercalciuria (3), but lack of response to low calcium diet, abnormal bone turnover, and, occasionally, borderline abnormal values of serum calcium suggest a different etiology. However, the more synthetic and clinically oriented classification recently proposed by Pak himself (4), i.e., hypercalciuria with hypercalcemia, or with high urinary sodium excretion, or absorptive and renal, sounds more useful. Actually, it would classify our patient again as having a mixed form of hypercalciuria, but characterized by high urinary sodium excretion and renal leak of calcium.
The Bataille and the first Pak classifications (1,2) did not adequately recognize the role of the high sodium intake in the pathogenesis of some forms of hypercalciuria, which is on the contrary clearly acknowledged by the recent Pak classification (4). Lack of recognition could depend on the well-known notion that patients with renal hypercalciuria show an exaggerated sodium urinary excretion when thiazides are given to block sodium reabsorption in the distal tubule (5). However, in our patient, the abnormal sodium urinary excretion was observed when he was not taking thiazides, suggesting that it was independent from the renal leak of calcium and overlaps it.
Our patient, therefore, shows the possibility that there is overlap between a primary tubular defect responsible for the renal leak of calcium (or a primary altered bone turnover), and a nutritional condition, the high sodium dietary intake, and this association induces, in turn, worsening of hypercalciuria. It was

only after addressing both conditions that treatment succeeded in reducing calciuria to the normal range, and in reverting secondary hyperparathyroidism. On the other hand, it is long known that the hypocalciuric activity of thiazides is maximized by the contemporaneous restriction of salt intake.

A diagnosis of primary hyperparathyroidism was advanced at baseline assessment of the patient because of the borderline high values of serum calcium and the hypercalcemic response to thiazide administration. However, PTH levels were normal as well as the US and nuclear scans. Furthermore, in primary hyperparathyroidism calcium phosphate is the major constituent of stones, while calcium oxalate, as in the present patient, predominates in renal hypercalciuria. We think that our patient, due to the very high hypercalciuria, presented an overstimulation of the PTH axis; at his first assessment this was not yet sufficient to give clearly abnormal PTH levels, but was already partially insensitive to calcium levels, as shown by the relatively increased PTH level during the thiazide-induced hypercalcemia. In the first year of follow-up, persistence of severe hypercalciuria worsened the condition leading to some escape from normal regulation of parathyroids, and thus to the clearly increased PTH levels. However, this process was still quite at the initial stage as shown by its reversibility after one more year of follow-up during which calciuria was successfully controlled, and by lack of demonstration of parathyroid abnormalities at the nuclear and US scans.

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