Idiopathic hypercalciuria hidden by primary hyperparathyroidism

Corrado Vitale
Emanuele Croppi*
Martino Marangella

Nephrology Unit and Renal Stone Centre, Mauriziano Umberto I Hospital, Torino, Italy
* Nephrology School, University of Florence, Italy

Address for correspondence:
Martino Marangella, M.D.
Nephrology Unit and Renal Stone Centre
Mauriziano Umberto I Hospital
Largo Turati, 62
10128 Torino, Italy
Ph. +39 011 5082424
Fax +39 011 5082425
E-mail: mmarangella@mauriziano.it

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Presentation of a clinical case

In October 1993, a 58-year-old man was referred to our hospital for recurrent calcium urolithiasis. Two of his first-degree relatives suffered from recurrent nephrolithiasis with idiopathic hypercalciuria.
The patient had passed six stones over the past 9 years, whose composition was calcium oxalate and phosphate. In 1992, he was treated with extracorporeal shock wave lithotripsy in order to remove a 10 mm sized stone from the left kidney, but the clearance of the fragments was not complete. When the patient was referred to our Nephrology Unit, he had few small calcifications in the lower pole of the left kidney and one little calcification in the higher pole of the right kidney.

Methods

According to our routine approach, biochemistries were performed on serum and urine samples, as follows.
Serum: total and ionized calcium (Ca), phosphate (PO_4), intact PTH, 25 hydroxyvitamin D (25 Vit D), 1.25 dihydroxyvitamin D (1.25 Vit D), alkaline phosphatase (ALP).
Twenty-four hour urine: supersaturations with calcium oxalate (βCaOx) and calcium phosphate (βbsh), estimated according to our program (1,2).
Fasting urine: Ca, creatinine (Cr), hydroxyproline (OHPro).
Ca excretion per Kg of body weight (Ca/Kg, mg) and Ca to Cr ratio (Ca/Cr, mg/mg) were calculated in 24-hr urine; Ca/Cr and OHPro to Cr ratio (OHPro/Cr, mg/g) were calculated in fasting urine.
Bone mineral density (BMD) was assessed by dual X-ray absorptiometry in lumbar spine.
Hypercalciuria was defined according to the following criteria: Ca/Kg ≥4 mg; Ca/Cr >0.20 mg/mg in 24-hr urine; fasting Ca/Cr >0.11 mg/mg (3-5).

Results

The high level of serum ionized Ca and the low value of serum PO_4 suggested primary hyperparathyroidism (PHPT). The diagnosis was confirmed by means of PTH and Vit D blood profiles and an ultrasound sonography that revealed an enlargement of the left basal parathyroid gland (Table I).
Basal BMD was significantly lower than normal (0.775 g/cm^2; T score: –2.87; Z score: –2.27) (6,7) (Table I).
The patient was submitted to neck surgery on January 1994 and a single parathyroid adenoma was removed (PTX). Blood ionized Ca levels lowered immediately after surgery (1.15 mmol/l) as well as intact PTH (26 pg/mL).
More details on mineral metabolism were obtained eight months after PTX (September 1994); the data were compared to those referring to pre-PTX phase (Table I). After PTX, serum Ca, PO_4, ALP, PTH levels and both fasting and daily Ca excretions were restored to normal. Consequently, also βCaOx and βbsh were reduced (4.7 vs 14.3 and 1.7 vs 5.2, respectively) after PTX.
Therefore all metabolic abnormalities responsible for calcium stone disease had reverted to normal on removal of parathyroid adenoma.
Concerning medical prescriptions, daily water intake of 2 litres at least was recommended, as well as controlled dietary intakes of sodium (100 mEq/day), protein (1 g/kg b.w., 50% of which animal protein) and Ca (1000 mg/day) (8-9).
One year later (September 1995), a relapse of hypercalciuria was detected (fasting Ca/Cr=0.23 mg/mg and Ca/Kg =3.5 mg). These data were confirmed in January 1996, together with nor-

Table I - Metabolic profile before parathyroidectomy (PHPT) and eight months after PTX.

			Before PTX	After PTX
Creat. Clearance		(mL/min)	85	78
Serum	total Ca	(mg/dL)	10.4	8.7
	Ionized Ca	(mmol/L)	1.44	1.15
	Phosphate	(mg/dL)	1.7	3.1
	Intact PTH	(pg/mL)	121	45
	ALP	(mU/mL)	281	188
	25 Vit D	(pg/mL)	18.4	16.4
	1.25 Vit D	(pg/mL)	40	36.7
24 hr urine	Ca	(mmol)	8.8	3.5
	Ca/Kg	(mg)	4.5	2
	Ca/Cr	(mg/mg)	0.28	0.12
Fast urine	Ca/Cr	(mg/mg)	0.25	0.05
	OHPro/Cr	(mg/g)	25.8	15.1
βCaOx			14.3	4.7
βbsh			5.2	1.7
BMC		(g/cm^2)	0.775	–
T-score			–2.87	–
Z-score			–2.27	–

mal PTH levels (38.2 pg/ml). The urinary excretion of sodium, total nitrogen and sulphate were even lower in 1995 than in 1994; this confirmed the dietary independence of hypercalciuria (1) and prompted us to prescribe a daily supplement of 12.5 mg of Hydrochlorothiazide + 2.5 mg of Amiloride (10,11).
Because of the low responsiveness of Ca excretion to such therapy (fasting Ca/Cr=0.18 mg/mg), the drug dosages were doubled up in January 1997. Thereafter, both daily and fasting urinary Ca excretions returned to normal values and remained stable until September 2003, as did the urinary supersaturation with Ca salts (Table II).
In 2003, BMD showed a 27% increase compared to 1994. Over the past nine years, ultrasound investigations showed neither formation of new renal stones nor accretion of the pre-

Table II - Metabolic profile after PTX.

			Years			
			1997	1999	2001	2003
Creat. Clearance		(mL/min)	84	109	99	94
Serum	Total Ca	(mg/dL)	9.1	9.9	9.4	9.5
	Ionized Ca	(mmol/L)	1.22	1.23	1.26	1.25
	Phosphate	(mg/dL)	2.9	2.3	3.4	2.4
	Intact PTH	(pg/mL)	38.2	48	–	51
	ALP	(mU/mL)	180	188	211	190
24 hr urine	Ca	(mmol)	4.8	2.7	3	3.8
	Ca/Kg	(mg)	3.1	1.5	1.7	2.2
	Ca/Cr	(mg/mg)	0.15	0.09	0.08	0.11
Fast urine	Ca/Cr	(mg/mg)	0.18	0.07	0.05	0.04
	OHPro/Cr	(mg/g)	8.4	12.6	13.9	13.4
βCaOx			7.1	3.9	–	2.1
βbsh			1.1	0.9	1.7	1.6
BMC		(g/cm^2)	0.911	–	–	1.16
T-score			–1.73	–	–	–1.03
Z-score			07	–	–	–0.61

existing ones.

Discussion

Primary hyperparathyroidism has been reported to occur in up to 5% of patients with idiopathic calcium stone disease. In these subjects hypercalciuria is considered as the main metabolic abnormality leading to urinary supersaturation. Alternatively, about 50% of idiopathic calcium stone formers are expected to have hyperparathyroid-independent hypercalciuria (1).
When our patient had the first metabolic evaluation after PTX, both fasting and daily Ca excretion were normal. This was the expected result of the removal of the calciuretic cause, that is, parathyroid adenoma. Relapse of hypercalciuria appeared unlikely unless hyperparathyroidism relapsed.
In the following year, an increase in urinary Ca was observed even in the absence of any abnormality of both serum ionized Ca and PTH levels. The hypercalciuria ensued from an increase of fractional excretion of the filtered Ca, as suggested by the increase of both fasting and daily Ca/Cr.
In order to explain our observations, we speculated that an increased Ca deposition in bone might have lowered Ca excretion for some months after surgical removal of the parathyroid adenoma. The "hungry bone syndrome", which frequently ensues from PTX for secondary hyperparathyroidism, was also described after surgery for PHPT (12). The prevailing bone deposition of Ca was confirmed by the 40% reduction of OHPro/Cr in association with the reduction of both fasting and daily urine Ca/Cr.
When the effect of the "hungry bone" subsided hypercalciuria relapsed, thiazides were able to restore both Ca excretion and urine supersaturation with Ca salts.
"Idiopathic" hypercalciuria may also occur in calcium stone formers with primary hyperparathyroidism.
The removal of parathyroid adenoma can induce a "hungry bone syndrome" which may temporarily alter renal Ca handling. Therefore, after parathyroid surgery, it is advisable to delay metabolic evaluation for many months to better define both the actual metabolic profile and the propensity towards urinary stone formation.
Present observations confirm that bone metabolism can play a significant role also in the pathogenesis of idiopathic hypercalciurias that are sensitive to thiazide therapy (13).

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