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Occasional Urinary Tract Infections and Urinary Depletion Effect Mask RTA and Carbonate-apatite Formation in a Strong Urinary Stone Former

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Abstract
We report on a female patient with severe bilateral urolithiasis. A once-off stone analysis performed in the past revealed Mg-phosphate. Occasional UTIs were considered to be the sole cause of stone formation. To date, this assumption had not been checked thoroughly, while stone formation in the patient steadily increased.

An inpatient metabolic and analytical work up was performed and stone-growth related urinary alteration was taken into account in urinalysis interpretation.

No UTI. NH_4Cl-loading test indicated RTA. CT revealed calculi in both kidneys. Carbonate-apatite (CAP) dominates stone composition. Computed urinary composition proximal to stones indicates hypercalciuria.

In this patient, occasional UTIs (pH) masked the causes of urolithiasis. Lack of updated stone analysis (CAP), metabolic work up (RTA) and improved urinalysis interpretation (hypercalciuria) concealed the true causes of stone formation.

Key words: stone analysis; urinary depletion effect; urinalysis interpretation; stone metaphylaxis

Abbreviations: CAP = carbonate hydroxylapatite; BRI = BONN-Risk-Index for calcium oxalate formation

Introduction

Updated stone analysis at any one time, extensive metabolic work up to clarify causes of stone formation at the initial stage of metaphylaxis, and regular control of urine and serum parameters to monitor treatment success are basic requirements in achieving optimum care in urolithiasis patients [1].

However, experience shows that even in strong stone formers with a long-time history of stone-related suffering, these requirements are often not met - to the disadvantage of the patient.

The present case of a severely suffering female stone patient shows the importance of an intensive metabolic work up including stone analysis, extensive urinalyses and improved data interpretation. Here, occasionally occurring urinary tract infections in the past were initially considered to be the sole cause of stone formation. For many years, this assumption was accepted by the practitioners without any further verification. At the same time, the patient's health status deteriorated.

Case Presentation and Management

We present a 41 year old female patient, BMI = 32 kg/m^2 (obese, WHO 1998), who has been severely suffering from recurrent bilateral urolithiasis since 2003, with focus on the left kidney. Family history indicates moderate osteoporosis in the maternal line (mother and grandmother). However, no urinary stone formation has been reported in these relatives.

Multiple stone removal surgeries (PNL, ESWL) were performed (Table 1). Although waste of stone material had been collected since 2003, only two stone analyses (by an unknown method) were carried out (Sept and Nov 2005) yielding 100% struvite and "mixed infect stone". During these three months only, the patient suffered from asymptomatic urinary tract infections elicited by Proteus mirabilis. In Oct 2003 and in Aug 2005, investigations of the differential kidney functions revealed each time a stable left vs. right kidney performance of 55vol% to 45vol%.

Detailed urinalyses to exclude a possible metabolic background for stone formation were not previously performed. The patient's nutrition has been imbalanced and poorly adapted to her stone disease, as no expert nutritional recommendations were provided up to now. Major identified nutritional problems include 1) hyper-energetic food, 2) excess intake of preserved phosphate-rich foodstuffs and beverages, convenience foods, 3) preference for soft drinks.

Since stone removal in Sept 2005, the patient suffers from pulmonary embolism, which is treated by low-molecular heparin. To date, no medications or any other recommendations for improved stone metaphylaxis have been given to the patient.

During metabolic work up, the urinary tract presented infection free.

Methods

In order to clarify the underlying metabolic causes of stone formation, an extended metabolic and analytical work up under controlled nutritional conditions was performed. This included 24h-urine collections and extensive urinalyses, Ca-loading test [2], parathormone

Table 1. The patient's stone history since the end of 2003. Stone compositions, and determination of the stone growth rates occurred between two observations. STR: struvite [wt.%], CAP: carbonate-apatite [wt.%]; a): "mixed infect stone" according to report. Stone size gives length(s) and perpendicular width(s) of stone(s) taken from planar X-ray, except CT. (*): staghorn calculus. Stone volume calculated as rotation ellipsoid. Further details see text.

Date	**Days passed**	**Total days passed**	**Procedure/ data source**	**Stone composition STR / CAP**	**Stone size (left) [cm]**	**Volume (left) [mm³]**	**Growth rate (left) [mm³/d]**	**Stone size (right) [cm]**	**Volume (right) [mm³]**	**Growth rate (right) [mm³/d]**
23/10/03	0	0	X-Ray		7.0 × 2.5(*)	64,141	æ	8.5 × 4.5(*)	170,235	–
Nov 03	23	23	surgery	70 30	7.0 × 2.5(*)	64,141	0	stone-free	0	0
Dec 03	30	53	report		7.0 × 2.5(*)	64,141	0	stone-free	0	0
10/02/04	57	110	X-Ray		8.5 × 4.5(*)	170,235	1,861	stone-free	0	0
22/04/04	65	175	surgery		stone-free	0	0	stone-free	0	0
Nov 04	214	389	report	80 20	1.0 × 1.0	2,094	10	stone-free	0	0
25/08/05	283	672	X-Ray		3.0 × 2.0 4.0 × 2.5 1.0 × 1.0	32,463	107	3.0 × 2.5	11,781	42
01/09/05	7	679	surgery	100 –	7.0 × 2.5(*)	64,141	4,525	stone-free	0	0
Oct 05	44	723	surgery		stone-free (relic)	0	0	stone-free	0	0
15/11/05	31	754	report	100 [a)] –	stone-free (relic)	0	0	stone-free	0	0
25/11/05	10	764	X-Ray		1.0 × 1.0 (relic)	262	26	1.0 × 0.2 1.0 × 0.2	210	21
15/12/05	20	784	native CT	80 20 60 40 5 95	2 calculi	832	**29**	2 calculi	258	**2**
			Mean	**48 52**			1310			22
			Median	– –			107			21

Table 2. (left)Typical urinary concentrations of lithogenic parameters in the patient's 24h-urine [mmol/l], collected in two fractions while staying under standardized and balanced nutrition according to the recommendations of the German Society of Nutrition. Estimated distal concentrations ci for different growth rates (30mm^3/d and 1,500mm^3/d) [6, 7] after application of the law of mass conservation using the present mean stone composition (48wt% STR, 52wt% CAP) and present growth period (20d). Urinary excretions [mmol/d] according to c, c_i(30mm^3/d), and c_i(1,500mm^3/d). No urinary tract infection was observed during hospitalization. (right) Results of metabolic test procedures and results of further analyses. BMD = bone mineral density; RTA = renal tubular acidosis; CAP = carbonate-apatite.

Period	**V [ml]**	**pH**	**Ca**	**Mg**	**PO_4**	**Uric acid**	**Oxalic acid**	**Citric acid**
08 h - 20 h	1450	5.97	1.58	1.80	8.4	1.71	0.160	1.016
20 h - 08 h	1280	6.00	1.52	1.84	10.9	1.09	0.141	0.605
total / mean	2730	–	1.55	1.82	9.6	1.42	0.151	0.823
c_i(30mm^3/d)	–	–	2.83	2.41	10.4	–	–	–
c_i(1,500mm^3/d)	–	–	34.58	17.41	37.4	–	–	–
excretion (uncorrected)	–	–	4.23	4.97	26.1	3.88	0.412	2.248
excretion c_i (30mm^3/d)	–	–	7.73	6.58	28.4			
excretion c_i(1,500mm^3/d)	–	–	94.4	47.5	102.0			

Method / Test	**Result**	**Finding**
Ca-loading test	blank: 0.114 load: 0.342	normal
parathormone	29 pg/ml	normal
osteodensitometry (Femur Neck BMD)	1.117g/cm^2	normal
ammonium chloride loading test	urinary pH >5.4	indication for RTA
Computerized tomography	2 calculi in each kidney left 832mm^3 right 258mm^3	progressive stone growth
IR-spectroscopy of stone material	struvite and CAP	increasing fraction of CAP (≤95 wt%)
BONN-Risk-Index for calcium oxalate	day: 0.6–1.61L^{-1} night: 1.5–2.1L^{-1}	moderate-increased risk increased-high risk

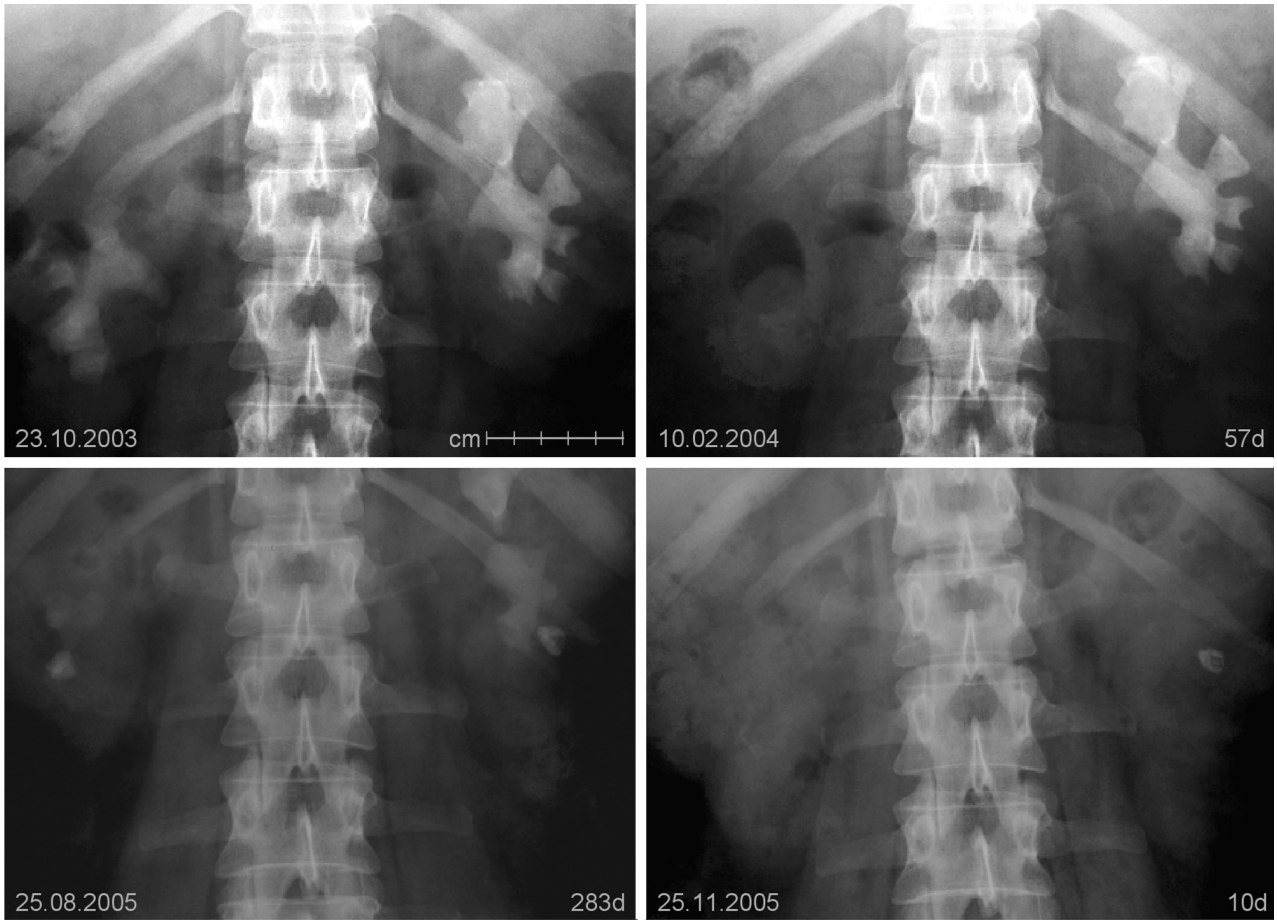

Fig. 1. X-ray photographs taken at different times clearly indicating the extreme stone growth rates taking place in the patient. Staghorn calculus formation within 57 days is demonstrated. The left kidney is more affected by stone formation than the right kidney. However, repeated investigations of the kidneys' differential volume function revealed a still normal situation: 55 vol% of urine is produced by the left kidney.

(PTH) determination, bone mineral densitometry, ammonium chloride loading test [3], BONN-Risk-Index for calcium oxalate formation (BRI) [4, 5], and computerized tomography (CT). Furthermore, IR-spectroscopy was conducted to identify the mineral phases in the stone material collected since 2003.

Urinary stones located in the urinary tract may substantially alter the urinary composition of lithogenic substances [6, 7]. As the patient suffers from extreme stone growth rates, we calculated a lower estimate of the concentrations of the lithogenic components proximal to stone material (i.e. the original composition from which stones were formed) from the voided urine's composition. Stone formation history is well documented by a number of plane abdominal X-ray pictures (Fig. 1).

The two-dimensional stone pictures obtained from X-rays are interpreted to reflect the projection of the outlines of a rotation ellipsoid defined by the lengths of the two longest perpendicularly correlated half-axes, a and b, with $a \geq b$. The stone's volume V is then calculated according to $V = (4/3)\pi a^2 b$. a and b were conservatively measured by micrometer.

Comparing two stone volumes obtained at different times, the (virtual) mean stone growth rate $\Delta V/t$ [mm^3/d] between both observations is calculated from the difference in stone volumes ΔV [mm^3] divided by the period t [d] between both observations. The non-altered concentration ci of a lithogenic substance can be estimated from the measured one according to the method described in [6, 7]. The Java-based computer program "Depletion V1.0" was used for all calculations [8].

Results

Table 2 shows a typical urinary composition voided by the patient. A urinary pH of around 6 coincides well with the general microbiological finding of an infection-free urine. The analyzed lithogenic substances' excretions, Ca*, Mg*, and PO_4*, reflect normo-calciuria, normo-magnesiuria, and normo-phosphaturia, as Ca* = 4.23 mmol/d, Mg* = 4.97 mmol/d, and PO_4* = 26.1 mmol/d.

Apart from a slightly decreased citric acid excretion, all other urinary (Na, K, Cl, SO_4, creatinine), and serum parameters (pH, pCO_2, pO_2, HCO3, BE) were non-pathological. Table 2 also gives the results of the different metabolic test procedures and the results of the further analyses. Remarkably, Ca-loading test, parathormone, and osteodensitometry showed no pathological alterations. Ammonium chloride loading

test, however, revealed strong indication for renal tubular acidosis (RTA). Repeated determinations of BONN-Risk-Index revealed a moderate to increased formation risk in the daytime (BRI 0.6–1.61L^{-1}) and an increased to high risk at night (BRI 1.5–2.1L^{-1}).

Native CT-scan evaluation of the kidneys yielded for both, the left and the right kidney, two calculi each with an overall volume of 1,090mm^3 (Table 1). Obviously, in both kidneys, stone growth had occurred during the last 20 days (25/11/05 – 15/12/05). Considering the left and right kidney's individual growth rates of approximately 29mm^3/d and 2mm^3/d, respectively, the (virtual) total average growth rate for the present growth period amounts presumably to 31mm^3/d.

Discussion

Although the mean growth rate used for c_i estimation (30mm^3/d) is much lower than the observed peak growth rate (>4,500mm^3/d, Tab. 1), the computed urinary depletion for Ca, Mg, and PO_4, amounting to approximately 45%, 24%, and 8%, respectively, is considerably, and, at least for Ca, non-negligibly high. Taking this into account in the urinalysis interpretation, a so far undetected hypercalciuria (Ca* >5mmol/d) may be a further underlying pathomechanism of stone formation in this patient.

Even when assuming a possible misestimating of stone volume towards too high values, the effect clearly remains considerable, in particular in view of the enormous peak growth rates obtained during previous staghorn calculi formation within a short period of only some weeks.

Choosing a realistic peak growth rate of e.g. 1,500 mm^3/d, the urine composition given in Tab. 2 would then reflect depletion in the lithogenic components exceeding 75% (PO_4). Although astonishingly high, this value is a conservative estimate based on a simple application of the law of mass conservation.

Despite perennially strongly recurring stone formation and amounts of sample material, no consequent and regular stone analyses were performed. Occasionally occurring urinary tract infections with urease-producing bacteria were considered to be the sole cause of stone formation. All practitioners accepted the initial assumption of pure struvite formation, although urinary pH values exceeding 7 were only rarely observed.

In fact, detailed stone analyses resulted in an increasing fraction of carbonate-apatite (CAP) with time. Presently, this fraction amounts up to 95wt%. Metabolic work up clearly diagnosed an underlying "incomplete RTA".

Consideration of the consequences of mass conservation in interpretation of urinalyses results in corrected urinary Ca-, Mg-, and PO_4-concentrations proximal to stone material of 2.83mmol/l, 2.41mmol/, and 10.41mmol/l, respectively. Thus, in contrast to the non-corrected analyses and taking into account a urinary volume of 2,730ml/d, at least, a (mild) hypercalciuria ($Ca^*_{(30mm^3/d)}$ = 7.73mmol/d) exists and should be taken into account in metaphylaxis strategy.

Hypercalciuria concomitant with RTA presents a typical situation promoting severe CAP formation. The occasional urinary tract infections have rapidly accelerated phosphate stone growth.

Retrospectively, it must be stated that in this patient, occasionally occurring urinary tract infections ("high pH") masked the true causes of stone formation.

Lack of careful analysis of stone material ("overlooked" CAP, "mixed infect stone") as well as the unexplainable omission of a sufficient metabolic work up ("overlooked" RTA) and analysis interpretation ("overlooked" potential hypercalciuria) increased the patient's suffering from recurrent stone formation.

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