Recurrent Nephrolithiasis in a Patient With Hypercalcemia and Normal to Mildly Elevated Parathyroid Hormone

Alexander Ritter, Rosa Vargas-Poussou, Nilufar Mohebbi, and Harald Seeger

Clinical Presentation

A 42-year-old man was referred to our stone clinic for recurrent episodes of symptomatic nephrolithiasis. Spontaneous stone passages occurred at the ages of 25, 40, and 42 years with one need for endoscopic stone removal. Calculi were composed of 100% calcium oxalate monohydrate. The patient had not taken any medication or supplements. Increased fluid intake was the only intervention for stone prevention. Metabolic work-up at presentation revealed mild hypercalcemia and normal to mildly elevated intact parathyroid hormone, even after repletion with oral 25-hydroxyvitamin D. 1,25-Dihydroxyvitamin D level and 24-hour urinary calcium excretion were within normal ranges (Table 1). Physical examination was unremarkable. Family history was negative for nephrolithiasis or hypercalcemia.

What are the main differential diagnoses of hypercalcemia with an elevated PTH level in this patient?

What tests help to distinguish between these two entities?

Which additional studies help to verify the diagnosis?

Discussion

What are the main differential diagnoses of hypercalcemia with a normal to mildly elevated PTH in this patient?

Hypercalcemia and high-normal or elevated PTH levels in the context of recurrent nephrolithiasis are strongly indicative of primary hyperparathyroidism (PHPT), which is a well-recognized cause of calcium oxalate stones. Urinary calcium excretion can be normal or elevated. Parathyroid surgery, which was considered in this case, is usually the treatment of choice for symptomatic patients. Ultrasound and nuclear imaging did not show evidence for parathyroid adenoma, which, however, does not rule out PHPT.

Familial hypocalciuric hypercalcemia (FHH) is a rare autosomal dominant disease that resembles PHPT, but is usually benign and not curable by parathyroidectomy. It is typically characterized by mild hypercalcemia, inappropriately normal or elevated PTH (in roughly 20% of patients), low urinary calcium, and a positive family history. FHH is genetically heterogeneous. It is caused by inactivating mutations in CASR, the gene encoding for the calcium-sensing receptor (CaSR) or in genes encoding two CaSR intracellular partner proteins. CaSR plays a major role in maintaining extracellular calcium homeostasis (Fig 1).

What laboratory tests help to distinguish between these two entities?

The calcium-creatinine clearance ratio (CCCR) helps to discriminate between PHPT and FHH in many cases, given that 24-hour urinary calcium excretion is often <100 mg/d in FHH and >200-300 mg/d in PHPT. In our patient, CCCR confirmed significant hypocalciuria with a ratio <0.01 (0.0096 at initial presentation, 0.0044 a month and a half later), suggestive of FHH. In PHPT, the ratio is usually >0.02. However, particularly in patients with PHPT and concomitant 25-hydroxyvitamin D deficiency or extremely low calcium intake, urinary calcium may be low-normal or low (CCCR ≤ 0.02; urinary calcium excretion < 200-300 mg/d). Of note, atypical FHH cases with CCCR > 0.01 (or even hypercalciuria) have been reported.

What additional studies help to verify the diagnosis?

Family screening can often establish the diagnosis of FHH owing to its high penetrance. Since FHH is usually asymptomatic, an active investigation for abnormalities of serum and urinary calcium should be performed if feasible, even if the family history is negative. Such an analysis could not be conducted in our patient’s family. Genetic testing is recommended in patients with atypical presentation (Fig 1), like our patient (nephrolithiasis, negative family history). Sequencing of CASR disclosed the patient was heterozygous for a previously described inactivating mutation (cytosine-to-thymine...
substitution at nucleotide 788 of the coding sequence, predicted to lead to a threonine-to-methionine substitution at amino acid 263 [c.788C>T p.Thr263Met].

It has recently been appreciated that FHH is not only a differential diagnosis of PHPT in patients with hypercalcemia and abnormally elevated PTH, but is also associated with kidney stones. In contrast to PHPT, literature about nephrolithiasis in the context of FHH is sparse and the underlying pathophysiology is not well understood, especially given the presence of hypocalciuria. In a French cohort, 21.7% of PHPT patients had a history of nephrolithiasis compared to 7.7% of patients with CASR mutations. Notably, all FHH patients with a history of nephrolithiasis were genetically identified as FHH type 1. In a study from Italy in which patients were selected for genetic testing based on clinical and biochemical compatibility with FHH, a history of nephrolithiasis was present in up to 67% of patients with CASR mutations. Furthermore, several studies, including a large genome-wide association study from Iceland, showed polymorphisms of the CASR gene regulatory region leading to reduced CaSR expression are associated with nephrolithiasis.

There is increasing evidence that the CaSR plays a complex role in contributing to the urinary equilibrium between inhibitors and promoters of calcium oxalate and phosphate precipitation. Downregulated tubular CaSR expression may impair dilution capacity, distal urinary acidification, and citrate production, while also increasing phosphaturia, thus resulting in calcium stone formation. In particular, decreased water excretion in the collecting duct and reduced citrate excretion in the proximal tubule could contribute to calcium oxalate precipitation. Future studies will have to further dissect the specific functions of the CaSR in different tubular segments that protect the kidney against negative effects of calcium salts.

This case explicitly illustrates that misdiagnosing FHH as PHPT as a cause for nephrolithiasis might have severe consequences, such as unnecessary parathyroidectomy. In stone formers with hypercalcemia and inappropriately normal or mildly elevated PTH,

### Table 1. Laboratory Test Results

<table>
<thead>
<tr>
<th>Laboratory Findings</th>
<th>Initial Presentation</th>
<th>+ 1.5 Months</th>
<th>+ 10 Months</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Blood</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium, mg/dL</td>
<td>10.7</td>
<td>11.0</td>
<td>11.0</td>
<td>8.4-10.2</td>
</tr>
<tr>
<td>Calcium ion, mEq/L</td>
<td>2.6</td>
<td>2.7</td>
<td>2.7</td>
<td>2.2-2.6</td>
</tr>
<tr>
<td>Magnesium, mEq/L</td>
<td>1.8</td>
<td>1.9</td>
<td>ND</td>
<td>1.3-2.1</td>
</tr>
<tr>
<td>Phosphorus (inorganic), mg/dL</td>
<td>2.2</td>
<td>2.7</td>
<td>3.2</td>
<td>2.7-4.5</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.0</td>
<td>1.0</td>
<td>ND</td>
<td>0.7-1.2</td>
</tr>
<tr>
<td>iPTH, pg/mL</td>
<td>64</td>
<td>63</td>
<td>117</td>
<td>15-65</td>
</tr>
<tr>
<td>25-Hydroxyvitamin D, ng/mL</td>
<td>17</td>
<td>ND</td>
<td>29</td>
<td>&gt;20</td>
</tr>
<tr>
<td>1,25-Dihydroxyvitamin D, pg/mL</td>
<td>48</td>
<td>ND</td>
<td>ND</td>
<td>&gt;26-95</td>
</tr>
<tr>
<td><strong>Urine</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Volume, mL/d</td>
<td>2,150</td>
<td>1,950</td>
<td>ND</td>
<td></td>
</tr>
<tr>
<td>pH</td>
<td>6.0</td>
<td>6.0</td>
<td>ND</td>
<td>5.0-7.5</td>
</tr>
<tr>
<td>Citrate, mg/d</td>
<td>430</td>
<td>626</td>
<td>ND</td>
<td>307-865</td>
</tr>
<tr>
<td>Oxalate, mg/d</td>
<td>20</td>
<td>32</td>
<td>ND</td>
<td>&lt;45</td>
</tr>
<tr>
<td>Phosphorus, mg/d</td>
<td>839</td>
<td>859</td>
<td>ND</td>
<td>400-1,300</td>
</tr>
<tr>
<td>Calcium, mg/d</td>
<td>160</td>
<td>81</td>
<td>ND</td>
<td>&lt;300</td>
</tr>
<tr>
<td>Magnesium, mEq/d</td>
<td>4.9</td>
<td>4.1</td>
<td>ND</td>
<td>6.0-10.0</td>
</tr>
<tr>
<td>Creatinine, g/d</td>
<td>1.55</td>
<td>1.69</td>
<td>ND</td>
<td>0.81-2.01</td>
</tr>
</tbody>
</table>

Conversion factors for units: calcium in mg/dL to mmol/L, ×0.2495; calcium ion in mEq/L to mmol/L, ×0.5; citrate in mg/dL to μmol/L, ×52.05; creatinine in mg/dL to μmol/L, ×88.4; magnesium in mEq/L to mmol/L, ×0.5; oxalate in mg/L to μmol/L, ×11.1; phosphorus (inorganic) in mg/dL to mmol/L, ×0.3229; 1,25-dihydroxyvitamin D in pg/mL to pmol/L, ×2.6; 25-hydroxyvitamin D in ng/mL to nmol/L, ×2.496.

Abbreviations: iPTH, intact PTH; ND, not determined.

### Different types of FHH:

- **FHH1**: CASR (calcium-sensing receptor)
- **FHH2**: GNA11 (G-protein subunit α11)
- **FHH3**: AP2S1 (adaptor-related protein complex 2, sigma subunit)

### Recommendation for genetic testing (most relevant examples):

- CCCR between 0.01 and 0.02 (without vitamin D deficiency)
- FHH phenotype, negative family screening
- Atypical presentation, family screening not feasible
- Familial form of hyperparathyroidism suspected

**Figure 1.** Overview of familial hypocalciuric hypercalcemia (FHH). Each type is caused by an inactivating mutation in the indicated gene. The calcium-sensing receptor (CaSR) mediates the negative feedback mechanism of extracellular calcium on renal calcium absorption and parathyroid hormone (PTH) excretion. Ga11 (encoded by GNA11) is involved in its signaling, while adaptor-related protein complex 2 (AP2) is essential for clathrin-mediated endocytosis. Some authors recommend genetic testing of the more common types first (FHH1 > FHH3 > FHH2). Abbreviation: CCCR, calcium-creatinine clearance ratio.
determination of CCCR may serve as a useful tool to differentiate between FHH and PHPT. If the diagnosis is in doubt, genetic analysis is recommended.

Final Diagnosis
Familial hypocalciuric hypercalcemia (FHH) with recurrent nephrolithiasis.

Article Information

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References


