Case Report

Transiently elevated parathyroid hormone-related peptide level associated with hypercalcemia and worsening renal insufficiency

Run Yu

Division of Endocrinology, UCLA David Geffen School of Medicine, Los Angeles, California, USA

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Abstract

An elderly female patient with multiple potential causes of hypercalcemia is described here. Transient hypercalcemia and elevation of parathyroid hormone-related peptide (PTHrp) level were found during a period of worsening renal insufficiency, both calcium and PTHrp levels returned to normal after renal function improved. The patient had no evidence of malignancy. This case suggests that PTHrp level may be elevated in worsening renal insufficiency in some patients and elevated PTHrp level does not always indicate malignancy in patients with hypercalcemia.

Keywords: hypercalcemia, malignancy, parathyroid hormone-related peptide, renal insufficiency

Introduction

Hypercalcemia is frequently encountered in clinical practice. Although the most common cause of hypercalcemia is primary hyperparathyroidism, many other causes of hypercalcemia exist, the most alarming of which are malignancies [1,2]. Humoral hypercalcemia of malignancy is mediated by parathyroid hormone-related peptide (PTHrp) secreted by the malignant tumors. PTHrp is a protein structurally and functionally related to parathyroid hormone (PTH); like PTH, PTHrp increases calcium reabsorption by the renal tubules and stimulates osteoclast activity, leading to hypercalcemia; unlike PTH, PTHrp does not upregulate renal synthesis of 1,25-dihydroxyvitamin D, the active form of vitamin D [1,2]. A patient with multiple potential causes of hypercalcemia is described here to illustrate that PTHrp level can be transiently elevated during acutely worsened renal insufficiency without evidence of malignancy.

Case

A 75-year-old female presented to the endocrine clinic for hypercalcemia and elevated PTHrp level. Four months before presentation, mild hypercalcemia (10.9 mg/dL, range 8.6-10.4) had been found by routine laboratory test (Table 1). Hypercalcemia persisted one month

Address for Correspondence: Run Yu, Division of Endocrinology, UCLA David Geffen School of Medicine, Los Angeles, California, USA.
E-mail: runyu@mednet.ucla.edu

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later; concomitant levels of PTH, 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D were all normal, but PTHrp level was mildly elevated (3.7 pmol/L, range 0.0-3.4). Her past medical history included hyperthyroidism, hypertension, hyperlipidemia and chronic renal insufficiency. Her creatinine levels had risen slightly (1.13-1.21 mg/dL with calculated glomerular filtration rate (GFR) 51-52 mL/min, from a baseline of about 1.0 mg/dL with calculated GFR 65 mL/min) in the several months before hypercalcemia was found and further rose to 1.32 and 1.47 mg/dL four and three months before presentation when hypercalcemia was found. Medications included methimazole, atenolol, chlorthalidone, lisinopril, nifedipine, spironolactone, rosuvastatin and aspirin. Review of systems was positive for fatigue, decreased appetite and weight loss of 10-15 pounds over several months. No signs of dehydration were recorded in the medical chart. Her thyroid-stimulating hormone (TSH) levels remained normal with methimazole treatment and serum protein electrophoresis and immunofixation electrophoresis did not find a monoclonal protein. Fluorodeoxyglucose-positron emission tomography (FDG-PET) did not identify any evidence of primary or metastatic malignancy. The calcium level dropped to high normal range (10.4 mg/dL) two months before presentation, along with a decrease in the creatinine level (1.11 mg/dL). The patient was still concerned of potential malignancy as suggested by elevated PTHrp level and presented to endocrine clinic four months after hypercalcemia was first found. Clinically she felt much better with improved appetite and weight gain. Repeat calcium and PTH levels remained normal and PTHrp level returned to normal (2.1 pmol/L) (Table 1).

### Table 1. Laboratory values

<table>
<thead>
<tr>
<th>Test</th>
<th>Reference range</th>
<th>4 months before presentation</th>
<th>3 months before presentation</th>
<th>2 months before presentation</th>
<th>Right after presentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium</td>
<td>8.6 - 10.4 mg/dL</td>
<td>10.9</td>
<td>10.8</td>
<td>10.4</td>
<td>9.9</td>
</tr>
<tr>
<td>Albumin</td>
<td>3.9 - 5.0 g/dL</td>
<td>4.5</td>
<td>4.4</td>
<td>4.4</td>
<td></td>
</tr>
<tr>
<td>Phosphorus</td>
<td>2.3 - 4.4 mg/dL</td>
<td>3.5</td>
<td>3.5</td>
<td>3.3</td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>1.4 - 1.9 mEq/L</td>
<td>1.7</td>
<td>1.7</td>
<td>1.5</td>
<td></td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.60 - 1.30 mg/dL</td>
<td>1.32</td>
<td>1.47</td>
<td>1.11</td>
<td>1.16</td>
</tr>
<tr>
<td>Glomerular filtration rate</td>
<td>&gt;89 mL/min</td>
<td>40</td>
<td>35</td>
<td>49</td>
<td>46</td>
</tr>
<tr>
<td>PTH, Intact</td>
<td>11 - 51 pg/mL</td>
<td>28</td>
<td>21</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Vitamin D,25-hydroxy</td>
<td>20 - 50 ng/mL</td>
<td>33</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitamin D,1,25-dihydroxy</td>
<td>19.9 - 79.3 pg/mL</td>
<td>23.0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PTHrp by LC-MS/MS</td>
<td>0.0 - 3.4 pmol/L</td>
<td>3.7</td>
<td>2.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td>0.3 - 4.7 mIU/mL</td>
<td>0.71</td>
<td>1.4</td>
<td>1.3</td>
<td></td>
</tr>
</tbody>
</table>

PTH: Parathyroid hormone, PTHrp: Parathyroid hormone-related peptide, LC-MS/MS: Liquid chromatography tandem-mass spectrometry, TSH: Thyroid-stimulating hormone

### Discussion

In this elderly patient with incidentally identified mild hypercalcemia, at least five potential causes of hypercalcemia need to be considered: primary hyperparathyroidism, thyrotoxicosis, dehydration, malignancy and renal insufficiency [1,2]. Primary hyperparathyroidism is unlikely with the normal PTH levels in the presence of chronic renal insufficiency [3]. The normal TSH and 1,25-dihydroxyvitamin D levels argue against thyrotoxicosis as the cause of hypercalcemia in this patient as hypercalcemia associated with thyrotoxicosis is typically accompanied by suppressed TSH and 1,25-dihydroxyvitamin D levels [4]. Dehydration is a possible cause of hypercalcemia due to decreased appetite, weight loss and use of chlorthalidone [5,6], but physical examinations did not describe signs of dehydration during the periods of hypercalcemia and she was still on chlorthalidone when hypercalcemia resolved. Malignancy is a concern due to the constitutional symptoms; the elevated PTHrp level further strengthens the suspicion and the normal 1,25-dihydroxyvitamin D level is also consistent with PTHrp-mediated hypercalcemia [2]. Her constitutional symptoms improved without specific treatment, however, and FDG-PET did not find any evidence of malignancy, making malignancy an unlikely cause of hypercalcemia in this patient. Acute renal insufficiency is a known cause of hypercalcemia [1]. It is known that the carboxy-terminal fragments of PTHrp are accumulated in renal insufficiency and cause false elevation of PTHrp levels if the PTHrp assay uses epitopes in the carboxy-terminus of PTHrp [7-9]. As
hypercalcemia can also cause acute renal failure, the false elevation of PTHrp level due to improper PTHrp assays in patients with hypercalcemia and renal failure may erroneously suggest humoral hypercalcemia of malignancy. It is thus important to use PTHrp assays targeting the amino-terminus of PTHrp or the intact PTHrp in patients with renal failure. The PTHrp test in this patient was performed at a reference laboratory (ARUP Laboratories, Salt Lake City, Utah, USA, test code 2010677) which uses a liquid chromatography tandem-mass spectrometry (LC-MS/MS) assay to measure PTHrp. According to the laboratory’s website (http://ltd.aruplab.com/Tests/Pub/2010677), this assay only measures intact PTHrp and is not interfered by amino- or carboxy-terminal fragments of PTHrp. In this patient without evidence of malignancy, as the intact PTHrp level is elevated in worsening renal insufficiency and returns to normal with improved renal function, the elevated intact PTHrp level may be caused by the worsening renal insufficiency and contribute to hypercalcemia.

Conclusion

PTHrp level may be elevated in worsening renal insufficiency in some patients and elevated PTHrp level does not always indicate malignancy in patients with hypercalcemia.

Conflict of interest

The author declares that he has no conflict of interest.

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References