Hypercalcemia in a Patient With Granulomatosis With Polyangiitis

Özant Helvacı, Merve Ecem Erdogan Yon, Hamit Kucuk, Abdurrahman Tufan, and Galip Guz

Clinical Presentation

A 48-year-old man presented to the rheumatology outpatient department with arthralgia and tinnitus, with a tentative diagnosis of otitis media. He reported difficulty walking for at least a month and was unable to walk for the last 2 days. Neurologic examination suggested a severe neuropathy. He was urgently admitted to the hospital with a preliminary diagnosis of vasculitis. A few hours later, he developed massive pulmonary hemorrhage and was intubated. A urinary catheter was placed, revealing macroscopic hematuria, which was followed by an anuric rapidly progressive acute kidney injury. He initially needed continuous kidney replacement therapy, which was later switched to intermittent hemodialysis.

A test for cytoplasmic antineutrophil cytoplasmic antibody (ANCA) directed against proteinase 3 ANCA was positive. Urine sediment contained countless erythrocytes (>5% acanthocytes), 10 to 15 leukocytes per high-power field in addition to granular and red blood cell casts. Computed tomography of the chest revealed extensive alveolar hemorrhage. These 2 findings, together with positive cytoplasmic ANCA, suggested the diagnosis of granulomatosis with polyangiitis (GPA). Urgent treatment with plasma exchange, pulse corticosteroids, and intravenous cyclophosphamide was initiated, along with numerous blood transfusions. Eventually, rituximab was added, and the patient achieved clinical remission.

The patient was transferred to a regular ward after 6 weeks of treatment in the intensive care unit, and serum creatinine level decreased to 1.2 to 1.3 mg/dL. After 8 weeks of hospitalization, he developed hypercalcemia with a calcium level of 12.0 mg/dL. Previous values were consistently in the low-normal range. Despite intravenous hydration and loop diuretics, serum calcium level increased to 15.5 mg/dL. Laboratory data are presented in Table 1.

Discussion

What is the differential diagnosis for this patient’s hypercalcemia?

The most common causes of non-parathyroid hormone (PTH)-mediated hypercalcemia are listed in Box 1.1,2 The patient’s laboratory studies indicated that hypercalcemia was not due to hyperparathyroidism or excess levels of active vitamin D, which has been rarely described in patients with GPA and is known to occur with other granulomatous diseases.3–5 The most frequent reason for hypercalcemia in hospitalized patients is malignancy-related hypercalcemia (MRH). PTH-related peptide (PTH-rP) is the culprit in 80% of cases. The remaining cases are due to bone metastasis (~20%) or humoral factors released from lymphomas (<1%).6 MRH is diagnosed with an elevated PTH-rP level, positive imaging results, or elevated 1,25-dihydroxyvitamin D level, respectively. The diagnosis of hypercalcemia due to medications requires a history of exposure and confirmation of elevated drug levels when possible. Miscellaneous infrequent causes such as steroid therapy withdrawal, acromegaly, and so on can be excluded on clinical grounds. Finally, for any patient with prolonged bed confinement, immobilization-related hypercalcemia (IRH) is a possibility.1

What is the most likely cause of this condition in this patient?

MRH is possible, but laboratory studies, including undetectable PTH-rP, do not support that diagnosis.

Table 1. Laboratory Parameters at the Time of Peak Hypercalcemia

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium, mg/dL</td>
<td>15.5</td>
<td>8.9-10.1</td>
</tr>
<tr>
<td>Ionized calcium, mmol/L</td>
<td>1.69</td>
<td>1.07-1.47</td>
</tr>
<tr>
<td>Phosphorus, mg/dL</td>
<td>2.6</td>
<td>2.5-4.5</td>
</tr>
<tr>
<td>Albumin, g/dL</td>
<td>3.3</td>
<td>3.5-5.0</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.3</td>
<td>0.6-1.1</td>
</tr>
<tr>
<td>PTH, pg/mL</td>
<td>2.5</td>
<td>15-65</td>
</tr>
<tr>
<td>PTH-rP, pmol/L</td>
<td>UD</td>
<td>&lt;2.0</td>
</tr>
<tr>
<td>1,25-Dihydroxyvitamin D, pg/mL</td>
<td>11</td>
<td>18-78</td>
</tr>
<tr>
<td>25-Hydroxyvitamin D, ng/mL</td>
<td>&lt;5</td>
<td>20-50</td>
</tr>
<tr>
<td>Thyroid-stimulating hormone, mIU/L</td>
<td>1.6</td>
<td>0.3-4.2</td>
</tr>
<tr>
<td>C-Reactive protein, mg/dL</td>
<td>2</td>
<td>0-6</td>
</tr>
</tbody>
</table>

Note: Testing for cytoplasmic antineutrophil cytoplasmic antibodies gave negative results. Conversion factors for units: serum creatinine in mg/dL to μmol/L, ×88.4; calcium in mg/dL to mmol/L, ×0.2495; phosphorus in mg/dL to mmol/L, ×0.3229.

Abbreviations: PTH, parathyroid hormone; PTH-rP, parathyroid hormone–related peptide; UD, undetectable.

• What is the differential diagnosis for this patient’s hypercalcemia?
• What is the most likely cause of this condition in this patient?
• How can the hypercalcemia be treated in the short and long term?
Immobilization-related hypercalcemia due to severe neuropathy caused by granulomatosis with polyangiitis.

How can the hypercalcemia be treated in the short and long term?

IRH will resolve with ambulation of the patient; however, in instances without the possibility of mobility, bisphosphonates and denosumab have been used with success.6,10

We enrolled the patient in an intensive physiotherapy program to ambulate him as much as possible. We did not want to use bisphosphonates and denosumab to avoid side effects such as prolonged hypocalcemia, jaw osteonecrosis, and atypical fractures given his potential for recovery.11 His hypercalcemia required 3 more hemodialysis sessions on alternate days. In the following week, with an increase in his mobility, calcium levels decreased to <10 mg/dL. He was discharged with a home physiotherapy program.

The patient received rituximab maintenance therapy for GPA for 2 years, which was ceased after confirmation of permanent disease remission, and has since been on drug-free follow-up. He is entirely ambulatory, with a creatinine level of 1.3 mg/dL and calcium levels within normal limits on his 5-year follow-up visit.

## Final Diagnosis

Immobilization-related hypercalcemia due to severe neuropathy caused by granulomatosis with polyangiitis.

## Article Information

**Authors’ Full Names and Academic Degrees:** Özant Helvacı, MD, Merve Ecem Erdogan Yon, MD, Hamit Kucuk, MD, Abdurrahman Tufan, MD, and Galip Guz, MD.

**Authors’ Affiliations:** Nephrology, Yıldırım Beyazıt University Yenimahalle Research and Training Hospital (OH); Internal Medicine, Diskapi Yıldırım Beyazıt Egitim ve Araştırma Hastanesi (MEYY); and Rheumatology (HK, AT) and Nephrology (GG), Gazi University, Ankara, Turkey.

**Address for Correspondence:** Özant Helvacı, MD, Yıldırım Beyazıt University Yenimahalle Research and Training Hospital, Department of Nephrology, Ankara, Turkey. E-mail: drozant@hotmail.com

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## References


