Reverse Pseudohyperkalemia in a Patient with Chronic Lymphocytic Leukemia

Taurino Avelar, MD

Abstract
A man, age 78 years, with a history of chronic lymphocytic leukemia presented to clinic for evaluation of a cough. On further evaluation, he was noted to have an elevated potassium level. This case report highlights the importance of distinguishing cases of true hyperkalemia from pseudohyperkalemia and reverse pseudohyperkalemia.

Introduction
Hyperkalemia can be challenging to manage. Differentiating true hyperkalemia from pseudohyperkalemia is often difficult. A less well-known condition that is thus challenging to identify is reverse pseudohyperkalemia. Here, I present an unusual case of reverse pseudohyperkalemia in an elderly man with a history of chronic lymphocytic leukemia (CLL).

Case Report
A man, age 78 years, with a history of CLL (not currently on treatment), chronic kidney disease 3A, coronary artery disease, and hypertension was initially seen in clinic reporting two days of coughing. He also reported one day of toe pain but was otherwise asymptomatic. There were no recent changes to his home medications, which included amiodipine, atenolol, aspirin, and pravastatin. Notably, he was not on an angiotensin-converting-enzyme inhibitor or an angiotensin receptor blocker, despite a history of coronary artery disease. Vital signs were within normal limits, and physical examination was unremarkable. Given his history of CLL, tumor lysis syndrome leading to gout was suspected. He was further evaluated, and laboratory results were significant for leukocytosis, 206 × 10⁶ cells/μL (95% lymphocytes) (normal 4.0 to 10.0 × 10⁶ cells/μL); plasma potassium, 8.4 mEq/L (nonhemolyzed; normal 3.5 to 5.0 mEq/L); calcium, 8.4 mg/dL (normal 9.0 to 10.5 mg/dL); phosphorus, 4.7 mg/dL (normal 3.0 to 4.5 mg/dL); uric acid, 10.6 mg/dL (normal 2.5 to 8.0 mg/dL); and glucose, 91 mg/dL (normal 70 to 100 mg/dL). Results were also significant for blood urea nitrogen, 36 mg/dL (normal 8.0 to 20 mg/dL); creatinine, 1.4 mg/dL (normal 0.7 to 1.3 mg/dL); and glomerular filtration rate of 49 mL/min/1.73 m². The patient’s baseline creatinine was 1.3 mg/dL, with a glomerular filtration rate of 53 mL/min/1.73 m². Given the profound leukocytosis, hyperkalemia, and hyperuricemia, tumor lysis syndrome seemed to have been confirmed. On the basis of the elevated plasma potassium level, the patient was subsequently referred to the Emergency Department for treatment.

Upon arrival, the patient’s repeat plasma potassium was 8.1 mEq/L. Electrocardiogram did not demonstrate peaked T waves, loss of P waves, prolonged QRS intervals, or evidence of high-grade block. He was treated with intravenous calcium gluconate, intravenous insulin, and oral sodium polystyrene sulfonate. Plasma potassium remained elevated at 8.1 mEq/L. A repeat electrocardiogram showed no change. With the exception of the cough and toe pain, he continued to be asymptomatic despite the persistently elevated plasma potassium, and he denied any weakness, fatigue, or palpitations. Given the apparent lack of improvement in potassium despite medical treatment, the decision was to proceed with emergent dialysis.

After partial dialysis, the possibility of reverse pseudohyperkalemia was considered. Potassium was rechecked, both the plasma and serum potassium, which were 7.9 mEq/L and 4.4 mEq/L, respectively. Given the patient’s history, hemodynamic stability, and lack of electrocardiogram findings and the fact that he was without improvement despite hemodialysis, it was suspected that the plasma potassium results did not represent the true in vivo potassium levels. Hemodialysis was subsequently discontinued, and repeat testing 4 hours later demonstrated similar results. The patient’s serum potassium was 4.4 mEq/L and 4.6 mEq/L on the day of discharge.

Discussion
Hyperkalemia is a life-threatening electrolyte abnormality that requires prompt diagnosis and treatment. In treating hyperkalemia, physicians have multiple therapeutic options at their disposal. In the case above, hemodialysis was felt to be an appropriate intervention because the patient’s plasma potassium level was not responding to medical management for severe hyperkalemia, a justifiable reason for emergent hemodialysis. Unfortunately, the inability to determine the patient’s true potassium level resulted in the implementation of interventions that could have led to significant morbidity and mortality. It was only after further clinical laboratory investigation that the true potassium level was identified (Table 1). Because there are various causes for falsely elevated potassium measurements, understanding the scenarios in which they may occur is crucial to a clinician’s decision making. The challenges in identifying this abnormality demand further discussion.
Potassium is normally measured from a sample of either plasma or serum. A sample of plasma is collected in a tube that contains heparin to serve as the anticoagulant (although it can also be collected with other additives, such as ethylenediamine tetra-acetic acid [EDTA] and citrate), whereas serum is collected in a tube that does not contain heparin or the other additives. In the clotting process, platelets undergo aggregation and degranulation while also releasing potassium. As a result, serum potassium is higher (0.36 ± 18 mEq/L) compared with a sample collected in plasma. This has also been noted in patients with significant erythrocytosis and leukocytosis. Such abnormalities can lead to what is known as pseudohyperkalemia, which is a phenomenon observed in vitro where the measured serum potassium is elevated and the plasma potassium is normal. In addition to these patient-related causes, there are additional factors that can lead to this abnormality (Table 2).

### Table 2. Causes of pseudohyperkalemia

<table>
<thead>
<tr>
<th>Factors</th>
<th>Examples</th>
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<tbody>
<tr>
<td>Mechanical</td>
<td>Prolonged tourniquet use&lt;br&gt;First clenching&lt;br&gt;Traumatic venipuncture or probing&lt;br&gt;Inappropriate needle diameter&lt;br&gt;Excessive force with syringe draws&lt;br&gt;Diameter mismatch of catheter, tube adapter device, and needle&lt;br&gt;Pneumatic tube transport/unpadded canisters&lt;br&gt;Specimen processing (vigorous mixing, excessive centrifugal force, prolonged fixed angle centrifugation or recentrifugation of gel separator tubes)</td>
</tr>
<tr>
<td>Chemical</td>
<td>Incomplete drying of ethanol containing antisepsics before venipuncture</td>
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<tr>
<td>Temperature</td>
<td>Specimens not stored at 15 °C -25°C</td>
</tr>
<tr>
<td>Time</td>
<td>Delayed processing</td>
</tr>
<tr>
<td>Patient related</td>
<td>Acute respiratory alkalosis&lt;br&gt;Thrombocytosis&lt;br&gt;Erythrocytosis&lt;br&gt;Leukocytosis/WBC neoplasms&lt;br&gt;Postsplenectomy state&lt;br&gt;Familial pseudohyperkalemia</td>
</tr>
<tr>
<td>Contaminants</td>
<td>Potassium-containing IV fluids&lt;br&gt;Tube additives containing potassium salts</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>Plasma reference ranges&lt;br&gt;Mislabeling</td>
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</tbody>
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IV = intravenous; WBC = white blood cell.

Potassium is elevated and the plasma potassium is normal. In a phenomenon observed in vitro where the measured serum potassium is elevated and the plasma potassium is normal. In addition to these patient-related causes, there are additional factors that can lead to this abnormality (Table 2). There have been attempts to define pseudohyperkalemia as a difference between serum and plasma potassium concentration of more than 0.4 mEq/L when the samples are obtained at the same time, remain at room temperature, and are tested within an hour of collection. Given the implications of basing medical decisions on falsely elevated levels, measuring potassium from plasma continues to be the preferred method.

In the case of reverse pseudohyperkalemia, the opposite is seen: plasma potassium is noted to be higher than serum potassium. It is a phenomenon that has been reported in patients with CLL. The mechanism of this phenomenon is yet to be clearly characterized, but several observations have been made. One possibility is increased sensitivity to heparin-mediated cell membrane damage during processing and centrifugation in the context of hematologic malignancy. In one study, the degree of increase in potassium was directly related to the amount of heparin contained within the tube into which the sample was collected. Mechanical stressors have also been implicated. Pneumatic tube transportation systems may lead to falsely elevated plasma potassium levels. These findings are not surprising given that the cells in patients with CLL are both fragile, and thus more susceptible to lysis, and more numerous, which can lead to significant abnormal laboratory results that may not otherwise be appreciated. This patient had a history of CLL with extreme leukocytosis, and the samples had been collected in heparin-containing tubes and transported via a pneumatic tube transportation system. No tested sample was transported manually for comparison.

There are ways laboratories may promptly identify cases of reverse pseudohyperkalemia. Consideration may be given to testing serum potassium if the plasma potassium is elevated in the context of leukocytosis. In addition, serum testing may include evaluating potassium in patients with CLL. Such testing may lead to prompt recognition of reverse pseudohyperkalemia. On further chart review, it was noted that the patient had not previously been started on an angiotensin-converting-enzyme inhibitor or an angiotensin receptor blocker because of previously elevated potassium levels, further highlighting the importance of making the diagnosis.

Because of its cardiotoxic potential, hyperkalemia is a potentially fatal electrolyte abnormality. The ability to differentiate true hyperkalemia from pseudohyperkalemia and reverse pseudohyperkalemia is crucial for determining the appropriate interventions. The necessary treatments can only be determined by taking into account the clinical history, hemodynamics, appropriate clinical laboratory investigation, and echocardiogram findings.

### Disclosure Statement

The author(s) have no conflicts of interest to disclose.

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### References


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CASE STUDY

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