CLINICAL VIGNETTE

Pseudohyperkalemia Due to Leukemia

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Introduction

Hyperkalemia is commonly diagnosed in hospitalized patients and can have serious cardiovascular consequences if serum potassium levels become severely elevated. Among the most serious complications of hyperkalemia are cardiac conduction abnormalities and cardiac arrhythmias, either of which can be acutely life-threatening.[1] Patients diagnosed with hyperkalemia with electrocardiogram (ECG) changes are often treated urgently due to the potential for cardiac arrest.[2] In certain clinical scenarios, hyperkalemia as reported by the laboratory may not truly reflect elevated serum potassium levels, a state referred to as pseudohyperkalemia.[3] In patients with pseudohyperkalemia, treatment for presumed hyperkalemia can lead to severely low serum potassium levels which can also manifest as dangerous cardiac arrhythmias. Clinicians should have a high index of suspicion in patients at risk for pseudohyperkalemia who develop otherwise unexplained "hyperkalemia" as reported by the laboratory. We will present a case of iatrogenic hypokalemia after treatment for pseudohyperkalemia.

Case Report

A 66-year-old male presented to the Emergency Department with facial and diffuse body rash that had progressed for several months. The rash was described as nodular, pruritic, and painful. It was most prominent on the trunk, upper extremities, and face; there was no mucosal or eye involvement. The patient denied fevers, chills, joint pains, shortness of breath, and chest pain. The patient had tried various topical ointments from his home country without noticing any improvement. His medical history was notable for essential hypertension, diabetes mellitus, and cutaneous T-cell lymphoma which was treated with chemotherapy several months prior to admission. PET-CT imaging showed progression of lymphoma despite treatment. Past surgical history included remote unspecified kidney surgery. Home medications were listed as dexamethasone, metformin, sitagliptin, and ertuglifozin. The patient denied alcohol, tobacco, and illicit drug use. Family history was remarkable for an unknown malignancy in his mother and sister.

Vital signs on admission were temperature of 36.3°C, blood pressure of 143/67 mmHg, heart rate of 109 bpm, respiratory rate of 18 bpm, and oxygen saturation of 97% on ambient air. Physical exam revealed a nodular, erythematous rash over the face, right neck, chest, abdomen, back, and groin. The rash was non-dermatomal without ulceration and unaffected areas of the skin appeared normal. Complete blood count was significant for white blood cell count of 34,230/uL, hemoglobin 13.0 g/dL, and platelet count of 103,000/uL. Basic metabolic panel was notable for mildly low sodium and bicarbonate but otherwise normal potassium, urea nitrogen, and creatinine. Routine SARS-CoV-2 PCR test done at time of admission was positive although the patient had no respiratory symptoms. Admission electrocardiogram (ECG) is shown in Figure 1A.

On admission, infectious evaluation including chest X-ray, urinalysis, and blood cultures were all normal results. The patient was treated with remdesivir to reduce the risk of severe COVID-19 disease. Hematology was consulted and initially recommended outpatient follow up until the patient developed laboratory studies concerning for tumor lysis syndrome. Additional labs included elevated potassium of 6.3 mmol/L and uric acid of 11.1 mg/dL. He was started on calcium gluconate, insulin, sodium zirconium cyclosilicate, and allopurinol.

Over the next several days, the patient's white blood cell count progressively increased, more than quadrupling from admission to 146,360/uL. During this period, the patient was persistently hyperkalemic on routine laboratory testing despite treatment to bring down potassium levels. When the patient's potassium reached a peak of 7.2 mmol/L, he was given two rounds each of furosemide, insulin, and sodium zirconium cyclosilicate. ECG done at the time is shown in Figure 1B. Subsequently, the patient developed a supraventricular tachycardia which terminated with adenosine. Additional blood analysis was done using whole blood that allowed the specimen to clot before centrifugation. This technique yielded a potassium level of 2.4 mmol/L and the patient supplemented with potassium chloride and stabilized. Figure 2 shows the correlation between potassium levels and white blood cell count.

Discussion

Pseudohyperkalemia has a myriad of causes, of which many are related to the technique used to draw the blood specimen and some of which are related to a patient's preexisting medical condition. Problems with specimen technique are typically related to *in vitro* red blood cell hemolysis. Common causes of this include use of a tourniquet with blood draws; having the patient clench their fist prior to the blood draw; forcibly squirting the blood through a needle; and excessive shaking of the collection tube after the blood is drawn.[4] Temperature and duration of time between specimen collection and laboratory

analysis can also affect potassium measurements. Warmer temperatures are associated with lower measured potassium levels. Higher temperatures cause increased sodium-potassium ATPase activity in the cellular membrane, which maintains lower extracellular potassium concentrations. Long specimen storage periods can also promote cellular destruction which can result in higher reported potassium levels.[5]

Several medical conditions also increase the risk of pseudohyperkalemia. Thrombocytosis and leukocytosis are associated with *in vitro* hyperkalemia due to the movement of potassium out of cells. Particularly relevant to this patient, severe leukocytosis is often due to hematologic malignancies which can also result in abnormally fragile white blood cells prone to lysis with minimal trauma. This phenomenon typically is associated with a total white blood cell count greater than 100,000/uL.[6]

In patients with severe leukocytosis where there is suspicion for pseudohyperkalemia, repeat blood specimens should be obtained that allows for testing serum potassium levels rather than the more conventional method of testing plasma potassium levels. The latter method uses collection tubes containing lithium heparin which can cause leukocyte lysis during the centrifugation process. Using a collection tube containing only gel separator without lithium heparin will allow the specimen to clot prior to centrifugation. The clotting is believed to stabilize cells in a fibrin matrix, thereby preventing their lysis, and allows for centrifuging the separated serum layer without contamination from the cellular component of blood.[6]

In patients with reported hyperkalemia without a clear cause, repeating the test may be indicated prior to treating with potassium-lowering agents. Given repeat testing will take additional time, electrocardiography can quickly provide additional information to further risk stratify the patient. The classic ECG findings associated with hyperkalemia include peaked T waves, shortened QT interval, prolonged PR interval, prolonged QRS duration, loss of P waves, and development of a sinusoidal pattern.[7] The medical literature yields mixed results in terms of the sensitivity and specificity of ECG changes in predicting hyperkalemia. Although ECG is neither sensitive nor specific in detecting hyperkalemia,[8] one study of 188 patients with severe hyperkalemia demonstrated 100% sensitivity for ECG predicting a short-term adverse event. This study assigned two blinded physicians to review each hyperkalemic patient's ECG and every patient with an adverse cardiac event had at least one of the following: peaked T waves, prolonged PR interval, prolonged QRS duration, heart rate less than 50 bpm, second or third degree heart block, junctional rhythm, or ventricular rhythm.[9]

Hypokalemia is also associated with its own ECG changes, including prolonged QT interval, the presence of U waves greater than 1 mm, and U waves with amplitudes greater than T waves in the same lead. U waves are more often seen in the lateral precordial leads when they are present.[10]

Conclusion

Derangements in serum potassium levels can have profound consequences including life-threatening arrhythmias. In patients with risk factors for pseudohyperkalemia without an apparent explanation for elevated potassium levels, further investigation is warranted prior to treatment with potassium-lowering agents. This should include obtaining a repeat specimen using a gel separator collection tube without lithium heparin to avoid *in vitro* cell lysis. Additionally, an ECG should be obtained to evaluate changes that could suggest true hyperkalemia or hypokalemia. In the patient described, there were no apparent reasons for him to develop hyperkalemia. Although the laboratory was reporting elevated potassium levels, his ECG was more concordant with hypokalemia. Optimal blood collection technique utilizing collection tubes that avoids cell lysis, and ECG evaluation of such patients might reduce the risk of treating spuriously elevated potassium levels leading to iatrogenic hypokalemia.

Figures

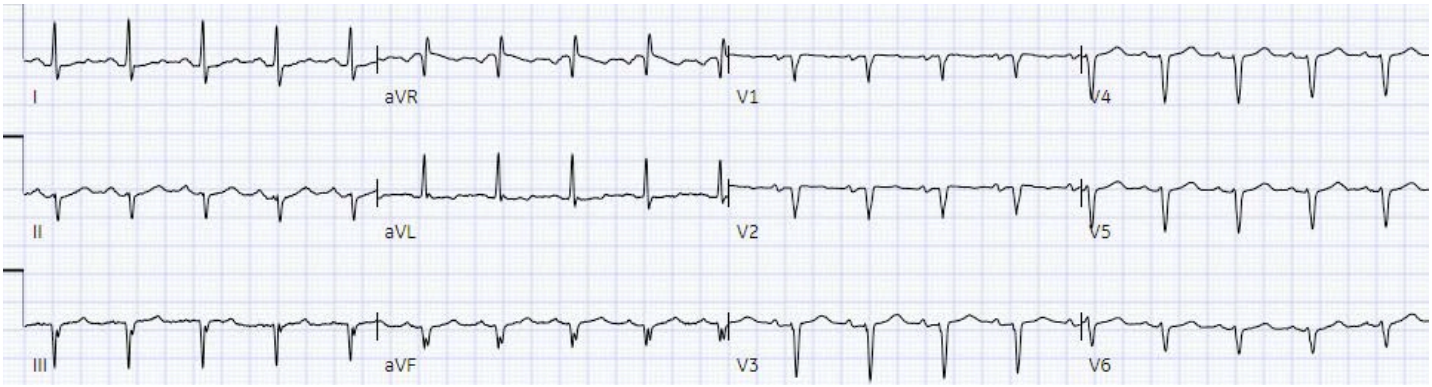

Figure 1A: ECG done at time of admission. Precordial leads V3 through V6 demonstrate T waves without U waves.

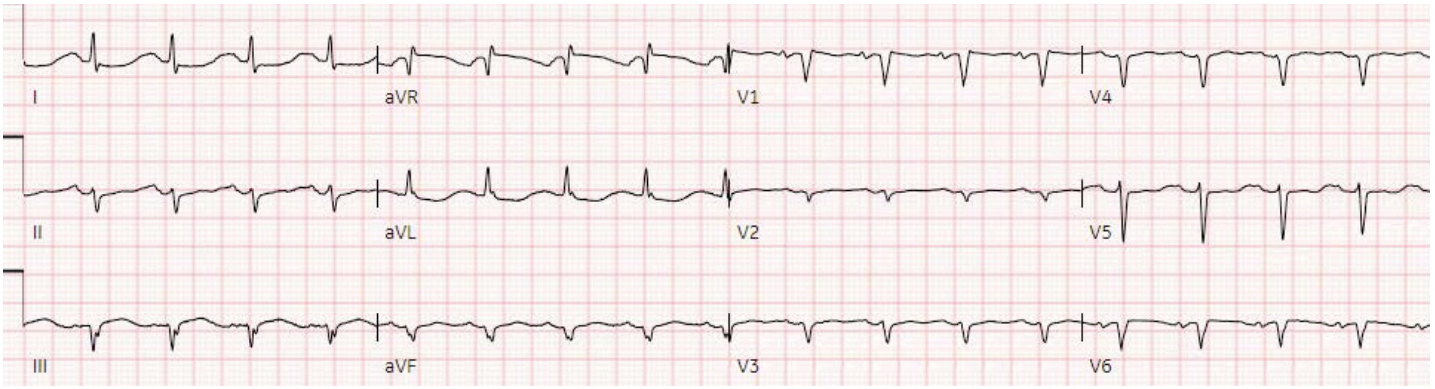

Figure 1B: ECG done while the patient had pseudohyperkalemia with actual underlying hypokalemia. There is diffuse dampening or loss of T waves when compared to admission ECG and faint U waves in precordial leads V3 through V6.

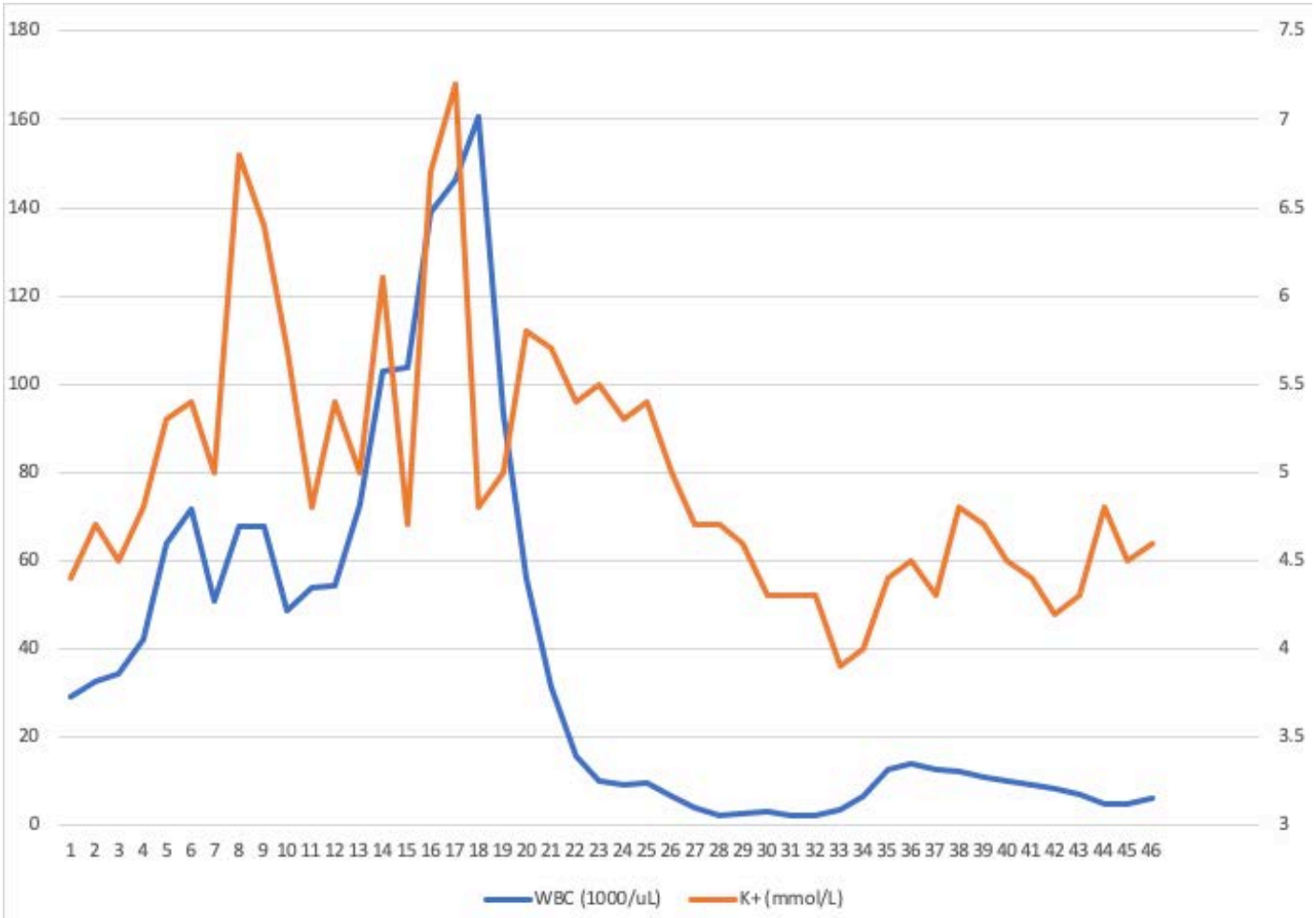

Figure 2: Graph of white blood cell (WBC) count and plasma potassium (K+) as reported by the laboratory using lithium heparin collection tubes versus hospital day.

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