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Case Report

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Unexplained hyperkalemia: The tip of the iceberg

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Summary

Background: Hyperkalemia is a potentially life-threatening medical condition; on the other hand pseudohyperkalemia is a benign entity, which should be suspected when serum potassium is elevated without concomitant electrolyte imbalances or remarkable degree of renal dysfunction. Patients seldom have the classical manifestations of hyperkalemia. Failure to recognize this condition causes anxiety among physicians, unnecessary laboratory testing and unwarranted treatments.

Case Report: We describe a sixty-year-old woman with persistent hyperkalemia and mean platelet count over a six-month period of 1015×10^3 cells/cumm. Based on this finding of thrombocytosis an immediate hematological evaluation has detected a myeloproliferative disorder, specifically essential thrombocythemia. Normalizing platelet count was paralleled by resolution of hyperkalemia.

Conclusions: Pseudohyperkalemia might be the tip of the iceberg to a major underlying pathological process. Unless a high index of suspicion to diagnose this disorder is maintained it will continue to be remarkably under diagnosed, subjecting patients to numerous unnecessary tests and treatments.

key words: **essential thrombocythemia • myeloproliferative disorder • pseudohyperkalemia**

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Background

Hyperkalemia is a potentially life-threatening medical condition which needs prompt identification and treatment. The final lab value of potassium is a byproduct of multiple factors including the technique of blood sampling, whether muscles were exercised prior and time lag to blood sample processing. Pseudohyperkalemia is defined as an entity in which there is an artifactual elevation of the serum potassium level due to *in-vitro* release of potassium from blood cell lysis [1]. It should be suspected when serum potassium is elevated without concomitant electrolyte imbalances or advanced renal disease. Patients seldom have the classical manifestations of hyperkalemia. However, failure to recognize this condition causes anxiety among physicians, in addition to unnecessary laboratory testing leading to unwarranted treatments (including dialysis), some of which are inconvenient and potentially harmful.

Case Report

A 60-year-old Caucasian female known to have chronic kidney disease stage 3, obesity, advanced chronic obstructive pulmonary disease and systemic hypertension who was found to be persistently hyperkalemic on a few occasions, with six month mean serum potassium levels of 5.6 meq/L (Reference Range (RR) at our laboratory 3.4–5.1 meq/L) (Plasma potassium estimation was not available in our local laboratories). She does not excessively consume high potassium dietary items or salt substitutes and her blood sample is taken with the assistance of a tourniquet. She was treated on several instances with sodium exchange resins without long-term improvement. She was also on angiotensin converting enzyme inhibitors, despite discontinuation of this and abandoning use of tourniquet hyperkalemia persisted.

On physical examination she was rather short in stature; blood pressure ranges between 100–140 systolic and 70–100 diastolic. No central cyanosis, or finger clubbing, jugular venous pressure not raised, no vascular bruits, breath sounds were quiet with bilaterally scattered wheezes. Cardiac and abdominal exam was essentially unremarkable and her lower extremities were edema free. No focal neurological signs or asterixis. Laboratory results -six month mean platelet count of 1015×10^3 cells (RR $130–430\times10^3$ cells/UL) with high normal hematocrit (53%) and red blood cell count (5.56 million/UL). However white blood cell count with differential was within the permissible limits (RR $4.0–11.3\times10^3$ cells/cumm). Mean serum creatinine over the last six months was 2.3 mg/dl (RR 0.5–1.1mg/dl) with GFR falling between 21–27 ml/min/1.73 m^2 body surface area (using Modification of Diet in Renal Disease equation). Serum sodium, chloride and bicarbonate were normal. Twelve lead resting electrocardiography was not suggestive of hyperkalemia. Referral to hematologist and subsequent evaluation findings were consistent with essential thrombocythemia: Carboxy-hemoglobin (7.7%; RR 0–5%), and polymerase chain reaction analysis for Janus Kinase 2 (V671F) mutation on bone marrow biopsy. With hydroxyurea therapy the mean serum potassium dropped and remained consistently below 5 meq/L.

Discussion

Hyperkalemia is a common medical emergency that manifests as neuromuscular and cardiac hyperexcitability, ranging from mild muscle cramps, weakness, and paralysis to extremely fatal dysrhythmias. On the contrary, pseudohyperkalemia is a phenomenon where serum potassium concentration is greater than that of plasma levels by an average of 0.4 meq/L without the classic clinical features of hyperkalemia, provided the samples are processed under ideal conditions [2]. A subtype of pseudohyperkalemia has been described as familial pseudohyperkalemia. It is an autosomal dominant disorder characterized by an inherent defect in red blood cell membrane potassium channels, which renders them to leak potassium when incubated at low temperatures particularly below 20° centigrade [3].

There is a lot of controversy regarding the most reliable sample indicated for identifying true *vs.* pseudohyperkalemia, (serum, plasma or whole blood). Traditionally for years serum has been used for estimation of potassium levels in biochemistry labs. However at M.D. Anderson cancer center, Texas, a premier cancer center in the world, plasma is the specimen of choice for potassium testing based on a recent study by Handy and Shen [4]. Sevastos et al [5] addressed this issue by introducing the Dk concept (difference between serum and plasma potassium levels) which regulates the relation between platelets and potassium in a mathematical fashion. They noticed that mean Dk is significantly increased in patients with erythrocytosis, thrombocytosis or combined disorders. Therefore, they concluded that plasma is the ideal specimen for potassium evaluation. On the contrary a study by Lee et al. [6] have had an opposite conclusion with serum/whole blood sample superior to plasma in diagnosing pseudohyperkalemia.

Hartmann and colleagues [7] in 1955 first identified patients with thrombocytosis to have "spurious hyperkalemia". They hypothesized this to be due to *in-vitro* lysis of blood cells during whole blood coagulation, which was later confirmed in several other studies. Over the next couple of decades many other investigators reported cases of pseudohyperkalemia in hematopoietic disorders like chronic lymphocytic leukemia (CLL), polycythemia vera, as well as secondary thrombocytosis from a variety of other etiologies. On the other hand there were reports of pseudohyperkalemia in patients with completely normal blood counts as suggested by few case reports [8] in the past. Paradoxically, not all patients with elevated cellular components exhibit this spurious hyperkalemia. Another possible mechanism is mechanical trauma to the cellular components of blood occurring either during the sample collection, transportation or time interval from collection to analysis, [9] which ideally should not exceed a maximum of six hours.

We believe that our patient had pseudohyperkalemia secondary to a myeloproliferative disorder (essential thrombocythemia) in view of the temporal relation between normalization of serum potassium and treating the platelet disorder. Despite the lack of availability of plasma potassium by our local lab, a relation between serum potassium levels and platelet counts was noticed, (Figure 1) this is in keeping with a previous report by Ong et al. [10].

The extent to which her erythrocytosis has contributed to this abnormality is unclear but probably minor. Perhaps it might not be unreasonable to directly measure plasma and serum potassium simultaneously in certain subsets of patients who

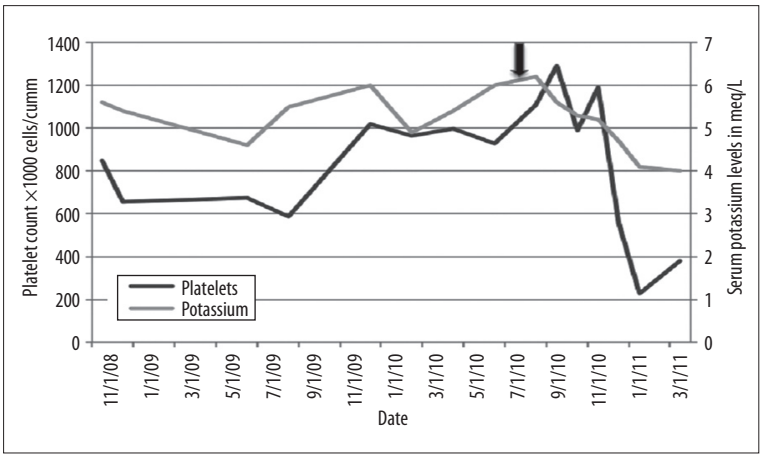

Figure 1. Relation between serum potassium (meq/L) and platelet counts (×1000 cells/cumm) with time. Arrow indicates the time (8/1/2010) when hydroxyurea was started.

are more prone to pseudohyperkalemia and our patient is no exception. In retrospect we feel that it would have been helpful to check plasma potassium level if it was available, but this should not delay a thorough, in-depth review of the clinical hematological and biochemical scenario to formulate an initial differential diagnostic work-up plan. This will facilitate earlier detection of more serious disorders such as hematopoietic malignancies, which will warrant immediate attention to prevent a wide array of complications.

Conclusions

Pseudohyperkalemia might be the tip of the iceberg to a major underlying pathological process. It should be on the top of differential diagnostic list when there is a discrepancy between serum potassium levels and renal function in the absence of precipitating factors (medications and hypovolemia). Physician's awareness about the mechanism and causation of pseudohyperkalemia is important to avoid potentially harmful treatments. Despite inconclusive evidence regarding the most accurate sample for estimation we suggest establishing a clinical laboratory liaison in the local areas to simultaneously measure plasma potassium and serum potassium in patients who have any predisposing factors (increased platelets or white blood cells) to pseudohyperkalemia. The importance of reliable methods of sample collection and if possible prompt processing of sample by the biochemical lab could not be emphasized and perhaps an educational program for phlebotomists in the United States regarding appropriate sampling to avoid this problem is warranted [11].

Conflict of interest

We declare that we don't have any financial disclosures or conflict of interests.

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