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Int J Case Rep Images 2020;11:101123Z01YA2020.
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Reverse pseudohyperkalemia: Verify potassium levels before initiating treatment

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ABSTRACT

Hyperkalemia is a complex laboratory abnormality. There are varying degrees of true hyperkalemia, pseudohyperkalemia, and even reverse pseudohyperkalemia which must be distinguished from one another. We present a case of reverse pseudohyperkalemia in an elderly male with a hematologic malignancy found to have an elevated potassium level on admission. Both plasma and serum levels were measured, plasma level was high while serum levels were normal, and a diagnosis of reverse pseudohyperkalemia was made. Awareness and increased suspicion result in rapid diagnosis, and prevent overtreatment and iatrogenic complications.

Keywords: Hyperkalemia, Pseudohyperkalemia, Reverse pseudohyperkalemia

How to cite this article

Ahmed Y, Rahman MU, Houston J, Al Jaber E. Reverse pseudohyperkalemia: Verify potassium levels before initiating treatment. Int J Case Rep Images 2020;11:101123Z01YA2020.

Article ID: 101123Z01YA2020

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Received: 27 January 2020
Accepted: 12 May 2020
Published: 26 May 2020

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doi: 10.5348/101123Z01YA2020CR

INTRODUCTION

Hyperkalemia is defined as K^+ levels greater than 5.0 mEq/L and is further classified as mild, moderate, and severe. Hyperkalemia is a potentially life-threatening laboratory abnormality that occurs in a number of conditions including renal failure, rhabdomyolysis, medication side effects, etc., and requires prompt diagnosis and treatment. It is crucial to differentiate true hyperkalemia from pseudohyperkalemia which is defined as an in vitro increase in the concentration of potassium in the serum without any electrolyte disturbances clinically [1–4]. This has been reported in condition resulting in lymphocytosis and/or thrombocytosis. Reverse pseudohyperkalemia is defined as a rise in the concentration of potassium in the plasma when the serum concentration is normal which is opposite to the phenomenon seen in pseudohyperkalemia and can be seen in conditions like chronic lymphocytic leukemia (CLL) [5, 6].

CASE REPORT

A 60-year-old African American male with history of diffuse lymphadenopathy currently undergoing evaluation at Hematology/Oncology clinic for underlying malignancy presented to the emergency department with hyperkalemia and concerns for possible tumor lysis syndrome (TLS). The patient denied any acute complaints and was hemodynamically stable on presentation. Physical exam was unremarkable except for pallid conjunctivae and diffuse lymphadenopathy. Initial labs revealed a hemoglobin 9.8 g/dL (13.5–17.5 g/dL), white blood cells (WBCs) >$440\times10^3/mm^3$ ($4000–11,000/mm^3$), creatinine (Cr) 0.7 mg/dL (0.6–1.2 mg/dL), no laboratory evidence of TLS, and a serum potassium (K^+) level of 7.3 mEq/L (normal 3.5–5.1 mEq/L). Electrocardiogram (EKG) obtained at presentation showed sinus rhythm without

peaked T waves. A venous i-STAT reported K^+ level of 8.1 mEq/L. Potassium levels were then checked in two different blood samples with serum K^+ level of 3.5 mEq/L and plasma K^+ levels of 6.2 mEq/L. An arterial i-STAT later confirmed K^+ level of 3.5 mEq/L. A Foley catheter was placed and confirmed adequate urine output (UOP). A diagnosis of reverse pseudohyperkalemia was made based on the above findings. K^+ was measured in serum samples thereafter for accurate measurement.

DISCUSSION

Hyperkalemia may cause nonspecific generalized symptoms, such as fatigue, nausea, vomiting, muscle weakness, and paresthesias. The most life-threatening effect of hyperkalemia is the effect on the myocardium. It must be quickly recognized and treated because of the high risk of lethal arrhythmias and cardiac arrest. On the other hand, identifying the presence of pseudohyperkalemia is crucial to avoid the complications caused by treating pseudohyperkalemia and thereby inducing actual hypokalemia [7, 8].

Markedly incorrect K^+ levels can occur in pseudohyperkalemia and reverse pseudohyperkalemia (also known as pseudo-pseudo-hyperkalemia). Pseudohyperkalemia is a well-recognized entity occurring when the serum K^+ levels are falsely elevated, and the plasma K^+ level is normal. Plasma and serum values are obtained from the liquid portion of the blood, however serum is the liquid after blood has clotted while plasma is the liquid obtained after clotting has been prevented using anticoagulant. The serum K^+ concentration normally exceeds the true value in the plasma by 0.1 to as much as 0.5 mEq/L due to K^+ release from white cells and platelets during the clotting process. Experts suggest a difference of 0.4 mEq/L between serum and plasma potassium concentration for consideration of pseudohyperkalemia (provided that both the samples were within an hour of collection and were kept at room temperature) [4, 9]. In such cases, the clinical decisions should be based on the plasma, not the serum K^+ concentration. Mechanical trauma during venipuncture (hemolysis) is the most common cause of pseudohyperkalemia. K^+ movement out of the cells (erythrocytes, leukocytes, or platelets) either during or after drawing of the blood specimen results in pseudohyperkalemia. The measured serum K^+ concentration may be falsely high (up to 9 mEq/L) in patients with marked leukocytosis (white cell count >70,000/mm) or thrombocytosis (platelet count >500,000/mm). With thrombocytosis, for example, the measured serum K^+ concentration rises by approximately 0.15 mEq/L for every 100,000/mm^3 elevation in the platelets count. Thrombocytes undergo degranulation and aggregation during the clotting process while also releasing K^+, thus leading to elevated serum K^+ concentration [2, 4]. The causes of pseudohyperkalemia are summed up in Table 1 [7]. The presence of pseudohyperkalemia should be strongly suspected whenever hyperkalemia and hemolysis, extreme leukocytosis, or thrombocytosis coexists. It should also be considered in the absence of apparent cause for the elevation in K^+ levels (impaired renal function, combination of K^+ raising drugs), in the absence of EKG changes and when there are no changes in muscle strength. It is worth mentioning that hyperkalemia is exceedingly rare if renal function is normal.

Reverse pseudohyperkalemia is a phenomenon opposite to what has been described earlier for pseudohyperkalemia, i.e., plasma K^+ levels are higher than serum K^+ levels (differentials based on serum and plasma K^+ levels are summed in Table 2). It is commonly seen in patients with hematological malignancies, especially CLL [9, 10]. The true underlying mechanism is unclear, however there are certain theories for the pathology behind this phenomenon based on the observations of the clinicians and the lab personnel. Routine serum analysis shows elevated measured potassium levels resulting from release of potassium from the fragile leukemic cells

Table 1: Factors causing pseudohyperkalemia [7]

Causes of pseudohyperkalemia	
Causative factors	**Examples**
Mechanical	Prolonged tourniquet use
	Fist clenching
	Traumatic venipuncture or probing
	Inappropriate needle diameter
	Excessive force with syringe draws
	Diameter mismatch of the catheter, tube adapter device, and needle
	Pneumatic tube transport/unpadded canisters
	Specimen processing (vigorous mixing, excessive centrifugal force, prolonged fixed angle centrifugation, or recentrifugation of gel separator tubes
Chemical	Incomplete drying of ethanol containing antiseptics before venipuncture
Temperatures	Specimens not stored at 15–25°C
Time	Delayed processing
Patient related	Acute respiratory alkalosis
	Thrombocytosis
	Erythrocytosis
	Leukocytosis/WBC neoplasms
	Postsplenectomy state
	Familial pseudohyperkalemia
Contaminants	Potassium-containing intravenous (IV) fluids
	Tube additives containing potassium salts
Miscellaneous	Plasma reference ranges
	Mislabeling

Table 2: Differentials of elevated potassium (K^+) levels

Condition	Serum K^+	Plasma K^+
Hyperkalemia	High	High
Pseudohyperkalemia	Falsely high	Normal
Reverse pseudohyperkalemia	Normal	Falsely high

during the clotting process. But in CLL, even the plasma levels of potassium are elevated. Severe leukocytosis leads to consumption of metabolic fuels that an impair Na-K ATPase activity, leading to release of potassium from a large number of white blood cells [11–14]. Spuriously elevated K^+ concentrations were seen with elevated white blood cell count in a longitudinal study [15]. Another proposed mechanism is the damage to the membrane of the millions of fragile malignant cells by the heparin in the tubes used for the collection of these samples [5, 9, 16]. In several studies, it was found that the K^+ level in plasma was higher in heparinized tubes than the K^+ levels obtained simultaneously in non-heparinized tubes and the extent to which the K^+ concentration was increased was proportionally related to the amount of heparin present in the tubes [6, 8]. Mechanical stressors can also attribute to the damage to these cells.

Figure 1: Tubes (vacutainers) for blood specimen collections.

Experts suggest a difference of 0.4 mEq/L between serum and plasma potassium concentration for consideration of pseudohyperkalemia or reverse pseudohyperkalemia, provided that both the samples were within an hour of collection and were kept at room temperature [4, 9].

Basically, our patient had normal renal function and good urine output. He had normal serum bicarb with no evidence of RTA and was not taking any potassium sparing diuretics. His white blood cell count was >440×10^3/mm^3 and he continues remained asymptomatic. It is well-known that one of the most common electrolyte disorders encountered in CLL patients is pseudohyperkalemia and so was the case in our patient.

The incidence and severity of the pseudohyperkalemia in chronic leukocytic leukemia was studied in over 300 patients with CLL listed in the Minnesota Tumor Registry between 1997 and 2014 [15]. So far, this is the first and only study to systematically look at serum and plasma potassium values in CLL patients, demonstrating that the results are related to pseudohyperkalemia. For every 10 × 10^9/L increase in white blood cell count, an increase in adjusted odds by 1.4 was observed. The median estimated percentage of patient's serum potassium elevation was 1.7% for WBC counts of 50 × 10^9/L, but when the WBC count was ≥100 × 10^9/L, it was considerably higher at 8.1% [15].

The different kinds of tubes for blood specimen collection and the color on the top of the tube is the code for the different chemicals in them (Figure 1):

1. Blue-top tube—Sodium citrate (Na citrate).
2. Lavender-top tube—EDTA.
3. Red-top tube—This tube has no anticoagulant.
4. Navy blue-top tube—There are two general types: one with K2 EDTA and one with no anti-coagulant.
5. Green-top tube—Sodium heparin or lithium heparin.
6. Serum Separator Tube (SST®)—This tube contains a clot activator and serum gel separator. It has no anticoagulant.
7. Grey-top tube—Fluoride.

Yellow/gold top can be used for sample collection to measure K^+ as it does not contain any chemical but delay in transport, nonoptimal temperature, and mechanical stressors can cause inaccurate results. ABG remains the analysis of choice and is an extremely quick and reliable test due to the shorter interval between drawing of the sample and analysis [17].

CONCLUSION

Presence of hyperkalemia with normal renal function, normal EKG, absence of clinical signs of hyperkalemia, absence of acid-base abnormalities and, in this case, the presence of extreme leukocytosis should raise suspicion for pseudohyperkalemia or reverse pseudohyperkalemia.

The exact mechanism of reverse pseudohyperkalemia in extreme leukocytosis is not clear. Initial approach involves getting serum and plasma potassium samples at the same time. A difference between serum and plasma potassium of more than 0.4 mmol/L is suggestive of pseudohyperkalemia or reverse pseudohyperkalemia. Arterial blood gas potassium might be the only accurate way to diagnose pseudohyperkalemia or reverse pseudohyperkalemia in such cases.

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Author Contributions

Yasir Ahmed – Conception of the work, Design of the work, Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Mustafeez Ur Rahman – Acquisition of data, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Jessica Houston – Acquisition of data, Analysis of data, Interpretation of data, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Emad Al Jaber – Conception of the work, Design of the work, Analysis of data, Interpretation of data, Drafting the work, Revising the work critically for important intellectual content, Final approval of the version to be published, Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved

Guarantor of Submission

The corresponding author is the guarantor of submission.

Source of Support

None.

Consent Statement

Written informed consent was obtained from the patient for publication of this article.

Conflict of Interest

Authors declare no conflict of interest.

Data Availability

All relevant data are within the paper and its Supporting Information files.

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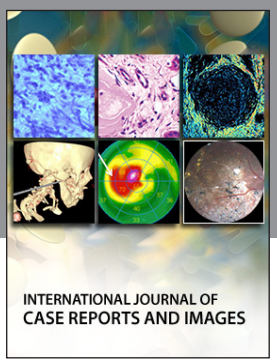

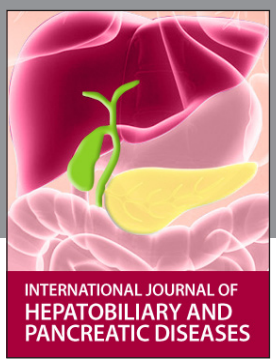

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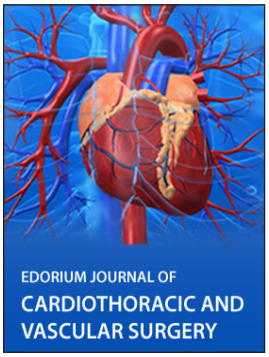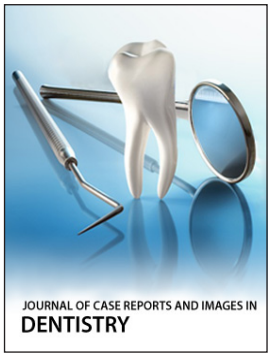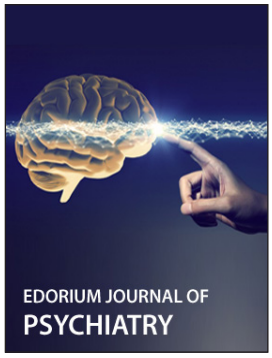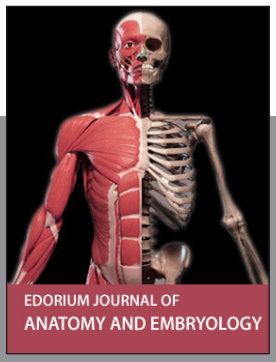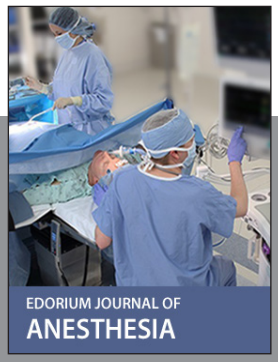
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