Ind J Clin Biochem (Apr-June 2021) 36(2):235–238
https://doi.org/10.1007/s12291-020-00889-3

CASE REPORT

Pseudohyperkalemia in Serum and Plasma: The Phenomena and Its Clinical Implications

Mala Mahto[1] · Mukunda Kumar[1] · Sushil Kumar[1] · Ayan Banerjee[1]

Received: 10 April 2020 / Accepted: 1 May 2020 / Published online: 14 May 2020

Abstract Hyperkalemia is a life threatening electrolyte derangement that must be recognized and treated quickly. Pseudohyperkalemia is defined as a difference between serum and plasma potassium concentration of more than 0.4 meq/L with serum values on the higher side when both the samples are obtained at the same time, remain at room temperature and are tested within 1 h of sample collection. Given the implication of basing medical decisions on falsely elevated potassium levels, timely identification of the entity of pseudohyperkalemia and differentiating it from true hyperkalemia becomes utmost important. Here we present a case report of a 36 year old female admitted with a provisional diagnosis of pyrexia of unknown origin with hepatosplenomegaly and anaemia under evaluation. During hospital stay her potassium levels in whole blood, serum and plasma reportedly differed significantly. An abnormal WBC count beyond assay range was reported and during subsequent investigations this lead to a peripheral smear being advised and diagnosis revealed chronic lymphoblastic leukaemia with blast crisis and 86% blast cells. In patients with leukocytosis and thrombocytosis, pseudohyperkalemia may exist in the absence of electrocardiogram changes or other clinical manifestations of true hyperkalemia thus leading to reevaluation of potassium values in serum, plasma and whole blood to arrive at the true picture.

Keywords Pseudohyperkalemia · Reverse pseudohyperkalemia · CLL · Leukocytosis thrombocytosis

✉ Mala Mahto
dr.malamahto@gmail.com

[1] Department of Biochemistry, All India Institute of Medical Sciences Patna, Phulwarisharif, Patna, Bihar 801507, India

Introduction

In healthy individuals normal serum potassium is defined as levels between 3.5 and 5 meq/L. In mild hyperkalemia serum potassium ranges from 5.1 to 6.1 meq/L. Serum potassium values in moderate hyperkalemia ranges from 6.2 to 7.0 meq/L and in severe hyperkalemia serum potassium values are more than 7.0 meq/L. Serum values are always noted to be higher than plasma because of the process of blood clotting essential for the recovery of serum which is associated with release of potassium from activated platelets. This difference does not exceed 0.4 meq/L [1]. A 36 year old female patient admitted in medicine ward for pyrexia of unknown origin presented with very high potassium values in serum not consistent with her clinical signs. An ABG sample of the same patient revealed potassium values within the normal reference range. In view of discrepancy between whole blood and serum values for potassium and no apparent manifestations of hyperkalemia, a detailed workup of the patient consisting of medical history, examination and analyses of all laboratory investigations done was deeply reviewed. It was noted that the WBC (white blood cell) count was very elevated (beyond assay range) and blast cells (86% with blast crisis) were noted on peripheral smear and a provisional diagnosis of CLL was made. Data was searched through internet for potassium values in such clinical settings and an entity of pseudohyperkalemia was identified as the most probable cause for such discrepancy between serum and whole blood values. Hyperkalemia is a lethal condition and calls for immediate intervention. However, hyperkalemia in absence of clinical signs and symptoms with no obvious cause for hyperkalemia such as kidney disease, acidosis, drug induced elevations etc. should always lead us to think of possible causes of spurious

potassium elevations. This entity termed pseudohyperkalemia is usually encountered on day to day basis in clinical biochemistry labs though cause for the same are many. Familiarity and timely identification of this condition and intervention depending on the cause along with optimum communication between lab and treating physician is the need of the hour so as to prevent inappropriate diagnosis and treatment.

Case Report

A 36 year old woman presented to the medicine OPD with history of fever with chills and rigor associated with headache, vomiting, decreased appetite and weakness since two months. There was sudden onset of breathlessness since 1 day. Past medical and surgical history were not significant. On examination she was found to be pale with tender hepatosplenomegaly. She was admitted in Medicine ward with provisional diagnosis of pyrexia of unknown origin with hepatosplenomegaly and anaemia under evaluation. She was advised further laboratory investigations to arrive at a probable diagnosis.

Lab Investigations

A serum potassium of 8.3 meq/L was noted in the absence of ECG changes or any clinical signs and symptoms. No other cause for hyperkalemia was also noted, hence a repeat serum potassium was advised which revealed a value of 10.3 meq/L. The ECG showed tachycardia and the patient was shifted from ward to High Dependency Unit (HDU) in view of her deteriorating condition as she started getting disoriented and highly irritable. Following this an ABG (arterial blood gas) was ordered which revealed potassium levels of 3.76 meq/L. A plasma sample with lithium heparin as anticoagulant was taken to evaluate potassium value which revealed potassium level of 7.3 meq/L. A Complete Blood Count (CBC) ordered at the same time revealed total leucocyte count beyond assay range. A peripheral smear suggested CLL with leukemic blast crisis with 86% of blast cells. Seeing discrepancy in potassium values in serum, plasma and whole blood in the setting of an elevated WBC count and no obvious identifiable cause of hyperkalemia a diagnosis of pseudohyperkalemia in serum and plasma was made.

What Happened?

It was after thorough review of patients with diagnosis of leukaemia with associated hyperkalemia in the internet that the diagnosis of spurious hyperkalemia was made. A significant difference between whole blood, serum and plasma potassium values in the setting of extreme leukocytosis in absence of clinical signs and symptoms points towards the probable diagnosis of pseudohyperkalemia and highlights causes responsible for the same.

Discussion

Potassium levels are measured in serum or plasma (collected in lithium heparin) or ABG syringe (whole blood) flushed with heparin. For serum estimation of K^+ levels, blood is collected in tubes containing no anticoagulant which is necessary for recovery of serum after clotting of blood. Therefore during clotting process platelets undergo aggregation and degranulation which releases potassium. This phenomenon is seen in vitro only. As a result serum potassium is higher (0.36 ± 0.18 meq/L) compared to plasma sample. The effects are more pronounced in leukocytosis and thrombocytosis [2]. Such abnormalities can lead to what is known as pseudohyperkalemia where the measured serum potassium values is elevated and the plasma potassium is normal. There is absence of ECG changes consistent with serum potassium measurement. This phenomenon was first reported by Hartmann and Melinkoff in 1955 as a marked elevation of serum potassium levels in absence of clinical evidence of dyselectrolytemia. He concluded that the high potassium in serum is due to leakage of potassium from platelets in vitro during the clotting process and same was confirmed in many studies thereafter [3]. In 1960, Nilsson et al. suggested that potassium could be released from other cellular components and assumed that red cells might be the source [4]. In 1966 Bronson et al. described 3 cases of psuedohyperkalemia in chronic myelogenous leukemia in transformation and concluded that the white blood cell breakdown could release potassium during coagulation [5]. Among patients with leukemia diagnosis, there is increase in plasma potassium with an increase in WBC count. An increase of 0.3 meq/L per 10^3 cells/μL in WBC count is most severe in CLL with an increase in plasma potassium of > 1 meq/L for every 100×100^3 cells/μL increase in WBC count [6]. When this case of CLL with extreme leukocytosis is analysed in particular it was found that the serum potassium values were consistently higher and even recorded to the extent of 10.3 meq/L. The sample was again collected as plasma in lithium heparin vacutainer and potassium levels were reported as 7.3 meq/L. When ABG sample was collected in a syringe containing lithium heparin anticoagulant and analysed as whole blood, potassium values were reported as 3.7 meq/L. The patient was diagnosed as chronic lymphoblastic leukemia with extreme leukocytosis depending on the reports of hematological investigations. Multifactorial etiology has been proposed

which is responsible for cell lysis causing release of intracellular K^+ [7]. There is increase in fragility of WBCs in CLL. Moreover there is disruption in ATP due to increase in WBC count which leads to shut down of Na^+ K^+ ATPase pump which is responsible for maintaining K^+ within the cell. As a result the extracellular potassium fails to enter the cell. The process of clotting during collection of blood sample in tubes without anticoagulant leads to aggregation of platelets and degranulation releasing potassium in the process from the cells in vitro. This phenomenon is more pronounced in leukocytosis and thrombocytosis [8].

Apart from this, another entity reverse psuedohyperkalemia is observed in patients with CLL where plasma potassium is higher than serum potassium (Table 1). One mechanism explaining this phenomenon is increased sensitivity to heparin mediated cell membrane damage during processing and centrifugation in the context of hematological malignancy. In one study the degree in increase of potassium was directly related to the amount of heparin contained in the tube into which sample was collected [9]. The cells in CLL are both fragile and numerous thus more susceptible to lysis which can lead to abnormal potassium values which may otherwise not be appreciated. The good side of the story is that the increased cell membrane fragility noted in CLL is due to presence of smudge cells which are diagnostic microscopic features of the malignant lymphocytes seen in CLL [10]. Smudge cells represent the irregular shape that the lymphocytes take when smeared onto glass slide for observation under microscope: it reflects a shape gained due to increased cell fragility. Several studies have shown that the percentage of the smudge cells present at diagnosis of CLL serves as a prognostic indicator with higher percentage of smudge cells associated with higher progression free survival and overall survival [11, 12]. It has been shown that higher vimentin expression which is an important cytoskeletal protein that contributes to the membrane rigidity is associated with lower percentage of smudge cells and worse prognosis in CLL [13]. Further CLL patients with mutated immunoglobulin heavy chain gene (IgV_H), a gene whose mutation is associated with better clinical outcomes were found to have a higher number of smudge cells than those with unmutated gene [14, 15]. An inverse relationship has been shown between smudge cell percentage and presence of CD38+ and ZAP-70+ both of which are unfavourable risk factors in CLL. Human CD38 is a pleiotropic membrane glycoprotein with ectoenzymatic properties mediating cell–cell interactions by binding the nonsubstrate CD31 ligand. CD38 is also a powerful negative prognostic marker for patients with CLL: $CD38^+$ CLL cells are characterized by a greater proliferative potential and by diminished sensitivity to chemotherapies. Together with CD38, ZAP-70, a member of the syk tyrosine kinase family, has recently been recognized as a reliable negative prognostic marker for patients with CLL [16]. An increased fragility and smudge cells presence is correlated, it is also postulated that the phenomena of reverse psuedohyperkalemia at the time of diagnosis may also have correspondingly higher overall survival.

Table 1 Differential diagnosis of hyperkalemia

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

What can be done in such cases by laboratory personnel and treating physicians?

The identification of the entity of pseudohyperkalemia is important and needs to be addressed otherwise treatment given in such cases may lead to iatrogenically induced hypokalemia.

As the entity occurs in haematological malignancies, tumour lysis syndrome resulting in high potassium values in vivo in such patients upon receiving chemotherapy may actually need treatment. Although initially the difference can be benign, as the tumour burden increases the degree of falsely elevated potassium can increase to levels that may lead to inappropriate management in an acute setting. Use of certain drugs which may have been a must could not be started in setting of unidentified pseudohyperkalemia.

The importance of avoiding the use the pneumatic tubes for transport of such specimens to prevent WBC lysis in patients with significant malignant leukocytosis: Best not shaken or stirred! [17].

To prevent wrong reporting of falsely elevated potassium values, we recommend placing of a precautionary note with such specimens of CLL from wards so that high potassium values are rechecked in serum, plasma and ABG sample which are hand delivered.

Amongst other commonly known reasons of pseudohyperkalemia are mechanical causes like prolonged tourniquet use, fist clenching, traumatic venipuncture, excessive force with syringe draws, pneumatic tube transport, mishandling during specimen processing like centrifugation etc. Adequate care to be taken during these processes so as to avoid falsely high reports.

Any sample sent for potassium estimation from i.v cannula of patients receiving potassium containing i.v fluids will also result in erroneous values on higher side. Similarly not maintain correct order of draw (Table 2) during phlebotomy or pouring/sending sample from/in a

Table 2 Phlebotomy: order of draw

Blood draw order	Tube cap colour	Description
1	Variable	Blood culture
2	Light blue	Sodium citrate
3	Red	Clot activator
4	Gold	Serum separator tube
5	Light green	Lithium heparin
6	Dark green	Sodium heparin
7	Lavender	EDTA
8	Grey	Sodium fluoride
9	Yellow	ACD solution

containing a preservative in the form of potassium salt like potassium EDTA in vacutainers for CBC estimation may also result in falsely high values [18, 19].

The phlebotomist stationed at outpatient departments or personnel entrusted with the sample withdrawing and transportation of blood samples in wards need to be enlightened about the chance of pre analytical errors in such cases and what can be done best to avoid them. Proper communication between laboratory personnel and treating personnel may also play an important role in overcoming preanalytical diagnostic errors and subsequent inappropriate treatment to a great extent.

Acknowledgements Department of Medicine, AIIMS Patna.

Author Contributions All authors 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.

Funding None.

Availability of Data and Material Not applicable.

Compliance with Ethical Standards

Code Availability Not applicable.

Conflict of interest None.

Consent for Publication Not applicable.

Informed Consent Informed consent taken from patient.

Ethical Approval Not required from Institute Ethics committee for case reports.

References

1. Asirvatham JR, Moses V, Bjornson L. Errors in potassium measurement: a laboratory perspective for the clinician. N Am J Med Sci. 2013;5(4):255–9.
2. Nijsten MW, de Smet BJ, Dofferhoff AS. Pseudohyperkalemia and platelet counts. N Engl J Med. 1991;325:1107.
3. Hartmann RC, Melinkoff AM. The relationship of platelets to the serum potassium concentration. J Clin Investig. 1955;34:938.
4. Nilsson IM, Skanse B, Bjorkman SE, et al. Platelet function in thrombocythemia. Acta Med Scand. 1960;167:353–68.
5. Bronson WR, DeVita VT, Carbone PP, Cotlove E. Pseudohyperkalemia due to release of potassium from white blood cells during clotting. N Engl J Med. 1966;274(7):369–75.
6. Colussi G. Pseudohyperkalemia in leukaemias. Am J Kidney Dis. 2006;47(2):373.
7. Sevastos N, Theodossiades G, Archimandritis AJ. Psuedohyperkalemia in serum: a new insight into an old phenomenon. Clin Med Res. 2008;6:30–2.
8. Colussi G, Cipriani D. Pseudohyperkalemia in extreme leukocytosis. Am J Nephrol. 1995;15(5):450–2.
9. Garwicz D, Karlman M, Øra I. Reverse pseudohyperkalemia in heparin plasma samples from a child with T cell acute lymphoblastic leukemia with hyperleukocytosis. Clin Chim Acta. 2011;412:396–7.
10. Mansoor S, Holtzman NG, Emadi A. Reverse pseudohyperkalemia: an important clinical entity in chronic lymphocytic leukemia. Case Rep Hematol. 2015;2015:930379. https://doi.org/10.1155/2015/930379
11. Johansson P, Eisele L, Klein-Hitpass L, et al. Percentage of smudge cells determined on routine blood smears is a novel prognostic factor in chronic lymphocytic leukemia. Leuk Res. 2010;34(7):892–8.
12. Nowakowski GS, Hoyer JD, Shanafelt TD, et al. Using smudge cells on routine blood smears to predict clinical outcome in chronic lymphocytic leukemia: a universally available prognostic test. Mayo Clin Proc. 2007;82(4):449–53.
13. Ivaska J, Pallari H-M, Nevo J, Eriksson JE. Novel functions of vimentin in cell adhesion, migration, and signaling. Exp Cell Res. 2007;313(10):2050–62.
14. Hamblin TJ, Davis Z, Gardiner A, Oscier DG, Stevenson FK. Unmutated Ig V(H) genes are associated with a more aggressive form of chronic lymphocytic leukemia. Blood. 1999;94(6):1848–54.
15. Kröber A, Seiler T, Benner A, et al. V_H mutation status, CD38 expression level, genomic aberrations, and survival in chronic lymphocytic leukemia. Blood. 2002;100(4):1410–6.
16. Deaglio S, Vaisitti T, Aydin S, Bergui L, D'Aerena G, Bonello L, et al. CD38 and ZAP-70 are functionally linked and mark CLL cells with high migratory potential. Blood. 2007;110(12):4012–21.
17. Smalley R, Cook S, Chan M. The case best not shaken or stirred! Chronic lymphocytic leukaemia and hyperkalemia. Kidney Int. 2010;77:167–8.
18. Sulaiman RA, Cornes MP, Whitehead S, Othonos N, Ford C, Gama R. Effect of order of draw of blood samples during phlebotomy on routine biochemistry results. J Clin Pathol. 2011;64:1019–20.
19. Gabriel LO, Giuseppe L, Gian LS, Martina M, Geraldo P, Gian CG. Incorrect order of draw could be mitigate the patient safety: a phlebotomy management case report. Biochem Med. 2013;23(2):218–22.