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Case Report

A Case of Reverse Pseudohyperkalemia in a Patient with Atypical Chronic Lymphocytic Leukemia

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Abstract

Reverse pseudohyperkalemia is a condition detectable in patients with hyperleukocytosis, defined as a plasma potassium concentration that is falsely high while the serum concentration is normal, that could lead to inappropriate treatment for patients. Here we report a case of a patient with atypical chronic lymphocytic leukemia, whose potassium and glucose blood levels allowed us to document a physiopathological genesis of reverse pseudohyperkalemia hypothesized, but not described in clinical practice. Pathological cells could have undergone death due to the exhaustion of the substrates necessary for survival, due in turn to the extreme hyperleukocytosis of the patient; this was probably due to increased usage and exhaustion of glucose to generate ATP for the Na^+/K^+-ATPase pumps.

Keywords: Chronic lymphocytic leukemia; Reverse psuedohyperkalemia; Hyperleukocytosis

Introduction

Hyperkalemia is a clinical problem that requires immediate recognition and treatment. However, in patients with elevated white blood cell counts, potassium levels detected could differ from the actual circulating levels, thus giving a pseudohyperkalemia, leading to the risk of inappropriate treatment for patients. Here we report a case of a patient who developed hyperleukocytosis during treatment with BTK inhibitor Ibrutinib, with the finding of reverse pseudohyperkalemia. Reverse pseudohyperkalemia is now defined as a plasma potassium concentration that is falsely high while the serum potassium concentration is normal [1-4]. In this case, we suggest an alternative way to detect this condition and hypothesize a new physiopathological genesis of this phenomenon.

Case Presentation

An 81-year-old male with a history of atypical chronic lymphocytic leukemia diagnosed 2 years prior, was admitted for balance disorders to the emergency department; complete blood count showed hyperleukocytosis (White Blood Cells (WBC) 423.7 K/μL) and mild anemia and thrombocytopenia (Hemoglobin (Hb) levels 9.6g/dl; platelet count 82 K/μL); plasma potassium (K^+) levels were increased at the admission (K^+ 7.5mmol/L, with normal values range 3.5-5 mmol/L) and lactate-dehydrogenase was increased (LDH 2239 UI/L). An Electrocardiogram (ECG) performed at admission was normal. The patient had been taking Bruton's tyrosine kinase inhibitor Ibrutinib at 420mg per dose for the previous 3 months, with an increment in WBC from 247.5 K/μL to 423.7 K/μL and a progressive anaemia and thrombocytopenia (Hb levels from 11.2g/dL to 9.6 g/dl; platelet count from 174 K/μL to 86 K/μL).

At the diagnosis, the patient had the following characteristics: CBC: Hb 10.9 g/dl, platelet count 212 K/μL, WBC 70.84 K/μL, absolute lymphocyte count 31.16 K/μL; serum LDH was 630 UI/L. FISH analysis revealed the deletion of 17p13.1 and trisomy 12; CT scan revealed splenomegaly (longitudinal diameter 17.2 cm) and multiple lymphadenopathies. Before the Ibrutinib he had received treatment with anti-CD20 agent Rituximab plus Bendamustine, obtaining a stable disease at the assessment at three and six months.

Given the presence of hyperkalemia (K^+ 7.5 K/μL), an arterial-blood gas test in a balanced heparin syringe was performed to assess whether the elevated K^+ levels were spurious or real. The arterial-blood gas test revealed diminished levels of K^+, thus configuring a clinical picture of "reverse" pseudohyperkalemia. To confirm it, two sequenced measurements on a plasma sample were performed (the first within 30 minutes of withdrawal), finding that, one hour apart one from another, K^+ levels increased from 3mmol/L to 8.6mmol/L. Glucose levels in these two analysis were respectively 81mg/dl and 10mg/dl. Even if ECG at the admission was normal, during hospitalization the patient developed paroxysmal atrial fibrillation, so therapy with Ibrutinib was suspended and pharmacological cardioversion with amiodarone was performed with success. After the cardioversion, given the progression with hyperleukocytosis, rapid lymphocyte doubling time, anemia and thrombocytopenia, a decision to begin therapy with oral Cyclophosphamide 100mg/day

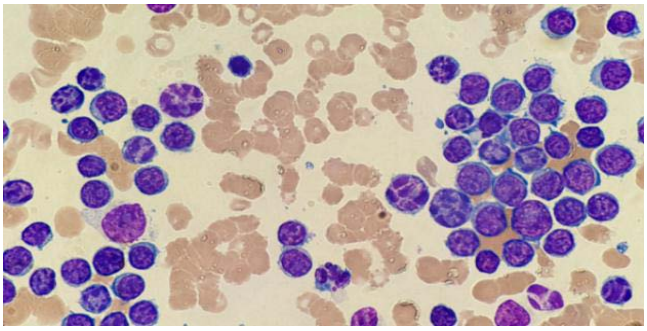

Figure 1: Peripheral smear morphology shows the presence of apoptotyc exhausted malignant cells.

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was made. Risk assessment for Tumor Lysis Syndrome (TLS) deemed the patient to be at medium risk due to his elevated lymphocyte count above 25 K/μL, but no tumor dimension of 5 cm or greater. TLS prophylaxis was already hydrated with intravenous fluids at 100mL/h and treated with allopurinol 300mg/day, and prednisone 12.5mg/day. After 4 days of observation with no side effects, the patient presented a syncopal episode and the ECG showed sinus rhythm.

Discussion

The new era of the targeted therapies has opened new scenarios that we have to take into consideration while approaching a patient. Ibrutinib has been proven to reduce malignant B-cell proliferation and survival, but also to induce lymphocytosis through the mobilization of lymphocytes into the peripheral blood [5]. TLS is a well-known risk of Ibrutinib treatment, and, despite prophylactic therapies, the incidence of TLS is still potentially life-threathning [6,7], and detecting hyperkalemia could be crucial to treat properly this kind of patients. Patients with leukemias/lymphomas and hyperleukocytosis frequently present with elevated K^+ levels that do not correlate with *in vivo* levels. These spurious values can be detected in serum samples with normal plasma K^+, generating the pseudohyperkalemia. Otherwise, another phenomenon has been recognized and described, "reverse" pseudohyperkalemia, which occurs when the plasma K^+ is falsely elevated in the setting of a normal serum and whole blood level.

Pseudohyperkalemia can be ascribed to several factors involved in almost every step of the analysing process, from the blood sample collection (i.e. leaving tourniquet on for extended time; excessive fist clenching; povidone-iodine contamination; EDTA contamination *via* inappropriate order of draw; drawing above intravenous infusion site; benzalkonium heparin contamination, used to coat catheters; vigorous mixing of tube contents; inappropriate collection technique such as traumatic venepuncture or small-gauge needle), to handling (i.e. chilling the specimen; re-centrifugation; transport through pneumatic tube system; delayed separation of blood cells from serum/plasma), to the very characteristics of blood constituents (as in familial pseudohyperkalemia, myeloproliferative disorders and thrombocytosis). Many mechanisms have been identified through which pseudohyperkalemia can be generated: hemolysis; release of K^+ from platelets or from leukocytes undergoing lysis during the clotting process; temperature-dependent K^+ leakage through the red blood cells; splenectomy; hyperventilation causing acute respiratory alkalosis [1,6-9]. The best-documented mechanism underlying reverse pseudohyperkalemia is, instead, the heparin-induced cell membrane damage and K^+ leakage in the setting of hematological malignancy, which leads to abnormally increased K^+ values only in plasma [10]. In 1982, another mechanism was suggested by JG. Logan and AC. Newland: studying leucocytes membranes from leukemic patients, in some of them was detected an increase of the Na^+/K^+-ATPase; subsequently there was an associated increase in the 'leakiness' of their malignant leukocytes membranes, and this led to *in vitro* hyperkalemia [11]. In this study, the alternative cause of reverse pseudohyperkalemia they postulated was that, in patients with hyperleukocytosis, a higher consumption of metabolic substrates by a high number of cells with more leaky Na^+-K^+-ATPase pumps, can result in a massive release of potassium. In the case reported, analyzing K^+ blood levels in two sequenced measurements on a plasma sample (one hour apart one from another), and performing an arterial-blood gas test in a balanced heparin syringe, allowed us to dose the real K^+ concentration, without the need to collect both serum and plasma samples. This could be due to a physiopathological genesis of the pseudohyperkalemia hypothesized years ago, but not yet documented in clinical practice. The patients glucose blood levels can be considered the litmus test of this phenomenon: they were normal in the arterial-blood gas test and in the first plasma detection, while the second measurement showed hypoglycaemia; this was probably due to increased usage and exhaustion of glucose to generate ATP for the Na^+/K^+-ATPase pumps. We thus suggest that, instead of dying from all the causes already described, pathological cells could have undergone death due to the exhaustion of the substrates necessary for survival, due in turn to the extreme hyperleukocytosis of the patient (Figure 1). Moreover, instead of detecting pseudohyperkalemia with serum and plasma samples, which may not be available in some hospital facilities and could take precious time to be performed, our experience showed that an arterial blood gas test in a balanced heparin syringe, much faster and more accessible, could help in the clinical practice to avoid inappropriate treatment in this setting of patients and to monitor K^+ levels in patients at risk of TLS.

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