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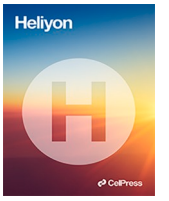

Case report

Analysis of a lung cancer case with transient pseudo hypoglycemia after PEG-rhG-CSF treatment

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ABSTRACT

Pegylated recombinant human granulocyte colony-stimulating factor (PEG-rhG-CSF) is an effective treatment for chemotherapy-induced neutropenia. However, it can also induce various adverse effects, including fever, bone pain, and other discomforts arising from the abnormal proliferation of blood cells. This study presents an analysis of a case involving a middle-aged patient with small cell lung cancer who exhibited transiently low blood glucose levels without experiencing any symptoms of hypoglycemia following PEG-rhG-CSF treatment. After thorough evaluation by clinicians and pharmacists, the condition was diagnosed as pseudohyperglycemia, a phenomenon distinct from true hyperglycemia. The article provides a pharmaceutical perspective on the contributing factors, mechanisms, and management strategies for pseudohypoglycemia, offering valuable insights for clinical practice.

1. Introduction

Neutropenia, a critical myelosuppressive adverse event caused by chemotherapy, significantly threatens patients by increasing their risk of infections and potentially leading to severe complications, including death. The variable severity and persistence of neutropenia often necessitate delays in chemotherapy administration and adjustments in drug dosages, further complicating cancer treatment [1,2]. To counteract neutropenia, granulocyte colony-stimulating factor (G-CSF) has been widely implemented in clinical settings. Evidence from a meta-analysis suggests that preemptive G-CSF administration can mitigate the risk of febrile neutropenia by over 50 % in patients with solid tumors, without substantially affecting tumor response or survival rates [3]. Among the available G-CSF formulations, pegylated recombinant human G-CSF (PEG-rhG-CSF) has emerged as a popular choice in clinical practice due to its long-acting nature and stable therapeutic effects [4]. However, the safety profile of this medication is not without its challenges, as it has been associated with a spectrum of side effects, including skeletal muscle pain, anaphylactic reactions, splenomegaly or splenic rupture, and leukocytosis [5]. Notably, the prophylactic use of G-CSF appears to heighten the risk of abnormal leukocyte elevation [6].

Pseudohypoglycemia, differently from hypoglycemia, refers to a condition where blood glucose measurements are lower than the actual levels. This condition is often misidentified as hypoglycemia without symptoms in clinical settings, thereby compromising clinical decision-making and escalating the risk of medication errors. This report presented an analysis of a unique case involving a

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suspected pseudohypoglycemia episode following PEG-rhG-CSF treatment, a phenomenon not previously documented in the literature. By reviewing and summarizing the etiologies and pathogenic mechanisms underlying pseudohypoglycemia, this study aimed to offer a reference for clinicians diagnosing and managing drug-induced pseudohypoglycemia.

2. Case report

The patient, a 47-year-old male, had been managing hypertension for over a year, with his condition well-controlled on levamlodipine besylate. He had a history of smoking 25 cigarettes daily and consuming 200 ml of alcohol three times weekly, but had abstained from these habits for more than two months prior to admission. A family history of lung cancer was noted, with the patient's father having suffered from the disease, although the specific tumor type remained undisclosed. In May 2023, the patient was diagnosed with limited-stage small cell lung cancer affecting the upper lobe of the left lung, with metastasis to the left hilar and mediastinal lymph nodes. Staging revealed cT2aN2M0, classified as IIIA. He underwent two cycles of EP chemotherapy in May and June 2023, experiencing grade IV myelosuppression (neutrophil count 0.33 × 109/L), which was managed with symptomatic treatment. Following concurrent chemoradiotherapy, he was admitted in July 2023. Upon admission, the patient reported intermittent chest pain, post-exertional fatigue, and diarrhea, but maintained regular eating and sleeping habits with no significant weight fluctuation. His Eastern Cooperative Oncology Group (ECOG) performance status (PS) score was 0.

On July 5, 2023, comprehensive biochemical tests, including liver and kidney function and blood glucose levels, were within normal limits: White blood cell (WBC) count was 6.3 × 109/L, red blood cell (RBC) count was 4.16 × 109/L, platelet (PLT) count was 286 × 109/L, and glucose (GLU) level was 5.11mmol/L. He received the first cycle of synchronous EP chemotherapy from July 7 to July 9, 2023, with Etoposide 160mg intravenously (ivgtt) on days 1–3 and Cisplatin 60mg ivgtt on days 1 and 2, followed by a 21-day cycle. On July 11, 2023, in light of his history of severe granulocytopenia, a subcutaneous injection of 6mg PEG-rh-CSF (manufactured by Qilu Pharmaceutical Co., LTD; lot number: 202211102KCH) was administered as a prophylactic measure. On the morning of July 12, a fasting blood sample was collected from the patient at approximately 7am and sent for laboratory analysis at 8am. The results were ready by 10am, revealing a venous blood glucose level of 1.84mmol/L, which is considered critically low, alongside a WBC count of 74.60 × 109/L; other parameters were unremarkable. A bedside consultation was promptly conducted, during which the patient reported a diminished appetite and a fasting period exceeding 12 hours prior to the blood test. The patient also ate little from 7am until 1pm, since experiencing side effects of nausea and vomiting caused by chemotherapy. At the time of consultation, the patient was alert, oriented, and exhibited normal limb muscle strength without any complaints. A rapid glucose meter was used to measure capillary blood glucose, yielding a reading of 7.8mmol/L. Given the clinical suspicion of pseudohypoglycemia, the patient's condition was closely monitored. After a two-day observation period without any further concerns, the patient was discharged with instructions to continue vigilant blood glucose monitoring and to consult with the local endocrinology department for any detected changes in blood glucose levels or islet secretion function. A graphical representation of the patient's treatment was provided in Fig. 1, while the monitoring of abnormal indicators detailed in Table 1.

3. Discussion

Hypoglycemia is characterized by a fasting blood glucose concentration in adults below 2.8 mmol/L, with diabetic patients exhibiting values below 3.9 mmol/L. This condition is typically accompanied by symptoms such as hunger, fatigue, sweating, tachycardia, and tremors, which are indicative of sympathetic nervous system activation. In extreme cases, hypoglycemia can lead to altered states of consciousness [7]. A subset of patients with hypoglycemia may not exhibit overt symptoms, a state known as "asymptomatic hypoglycemia," which is more prevalent among individuals with longstanding diabetes and is associated with impaired

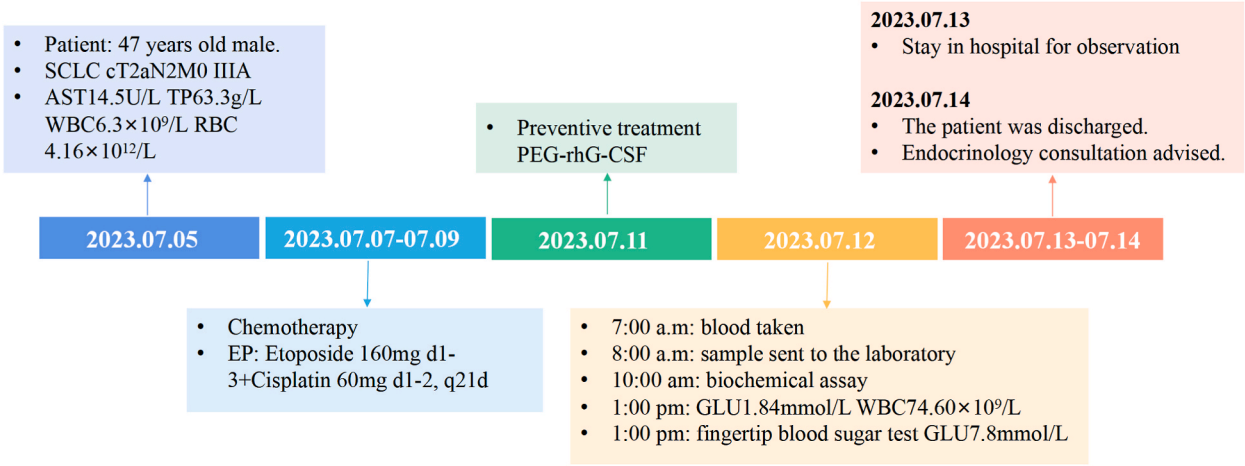

Fig. 1. Patient treatment process.

Table 1
Blood routine test and blood glucose monitoring values of patients.

Date	WBC count ($\times 10^9$/L)	RBC count ($\times 10^{12}$/L)	PLT count ($\times 10^9$/L)	Venous blood glucos (mol/L)	Fingertip blood glucose (mmol/L)
2023/7/5	6.3	4.16	286	5.11	–
2023/7/12	74.6	3.77	209	1.84	7.8
2023/7/18	6.79	3.57	89	6.02	–
2023/8/11	5.34	3.8	251	–	–
2023/8/18	5.1	3.6	197	6.68	–
2023/8/25	5.34	3.8	251	6.05	–
2023/9/12	3.50	3.8	257	6.04	–

sympathetic nerve function and the body's hypoglycemia detection capabilities. Distinguishing "asymptomatic hypoglycemia" from "pseudohypoglycemia" is essential and often requires careful clinical assessment in line with the Whipple triad [8,9].

3.1. True hypoglycaemia factors

3.1.1. Drug factors

Hypoglycemia is a frequently observed adverse effect associated with the use of hypoglycemic medications, including insulin, sulfonylureas, and insulin secretagogues. These instances are indicative of true hypoglycemia. Research indicates that the incidence of mild to moderate hypoglycemic episodes can reach up to 30 % among patients utilizing insulin or sulfonylurea medications [10].

3.1.2. Physiological and psychological factors

Moreover, factors such as mood, physical activity, and dietary habits can significantly influence blood sugar levels. For instance, a state of high anxiety can stimulate the sympathetic nervous system, leading to increased secretion of adrenaline and norepinephrine, which in turn can elevate blood sugar levels. Prolonged exercise or insufficient food intake can also lead to hypoglycemia [11]. These factors are generally associated with true hypoglycemia and are less likely to result in clinical misdiagnoses. They can be clearly identified through appropriate assessments, minimizing the risk of erroneous clinical judgments.

3.2. Pseudohypoglycemia factors

"Pseudohypoglycemia" occurs when the measured glucose level—below 2.8 mmol/L—is erroneously lower than the actual whole-body glucose level, without any clinical manifestations of hypoglycemia, and with a normal capillary blood glucose retest [12]. While false hypoglycemia is often linked to diseases, detection errors, and other factors, drug-indirectly induced cases are less common. The condition's pathogenesis is primarily linked to the in vivo and in vitro glycolysis of glucose, and there is no specific diagnostic marker for its identification. This discussion focuses on the pseudohypoglycemia associated with the present case and explores the potential causes as detailed below.

3.2.1. Disease factors

Pseudohypoglycemia has been predominantly reported in cases with abnormal increases in blood cells, such as myelodysplastic tumors, leukemia, and polycythemia vera. These conditions are characterized by heightened tissue glucose consumption and a significant reduction in venous blood glucose levels compared to arterial and capillary glucose concentrations, explaining the absence of hypoglycemic responses [13–15]. Studies have also demonstrated that elevated hexokinase (HK) activity in the red blood cells of polycythemia vera patients can intensify glycolysis, resulting in pseudohypoglycemia [16,17]. Additionally, peripheral circulatory disorders caused by Raynaud's syndrome and shock can lead to a spurious decrease in fingertip blood sugar while leaving venous blood sugar levels unchanged, causing false hypoglycemia.

3.2.2. Test method factors

The current standard methods for assessing biochemical blood glucose in hospitalized patients involve the use of glucose oxidase (GOD) and hexokinase (HK) assays, both of which require venous blood samples. These testing methods are subject to various influences, including sample storage conditions, processing time, patient emotional state, and the duration of fasting. It is noteworthy that the rate of glucose consumption is positively correlated with both the storage duration and temperature of the blood samples. Studies have shown that the glucose concentration in blood samples to be centrifuged will gradually decrease over time due to erythrocyte catabolism, bacterial metabolism or leukocyte enzymatic hydrolysis [18,19]. Moreover, the glucose oxidase (GOD) assay is susceptible to interference from reducing substances such as ascorbic acid and reduced glutathione. These agents can interact with the hydrogen peroxide (H2O2) byproducts of the GOD reaction, leading to a reduction in H2O2 levels and consequently yielding spuriously low measurements of blood glucose levels [20]. Conversely, the HK method is less susceptible to external factors such as mild hemolysis, hyperlipidemia, vitamin C, and EDTA blood anticoagulant, offering greater accuracy and often being the preferred reference standard for blood glucose measurements. However, the HK method's specificity in detecting blood sugar can be compromised by elevated levels of low-density lipoprotein (LDH), which may result in falsely low readings. Special caution is needed when employing the HK method in patients with acute and chronic liver diseases or myocardial diseases that exhibit increased LDH levels [21,22].

4. Incidence of pseudohyploglycaemia in the literature

Research indicates that the clinical detection value of blood glucose remains relatively stable for up to 2 hours following the storage of blood samples; beyond this timeframe, the detection value may diminish, which was not the case for this particular patient [23]. Upon re-evaluation of the patient's clinical presentation, laboratory findings, and medication history, it was deduced that the administration of PEG-rhG-CSF might have triggered a rapid and substantial increase in white blood cell count, subsequently leading to excessive glucose consumption and, consequently, a lower blood glucose detection value. Literature suggests that an abnormal rise in white blood cells is typically observed within 1–4 days post-PEG-rhG-CSF treatment [24–26]. Furthermore, the presence of elevated white blood cells could potentially precipitate instances of false hypoglycemia. A retrospective analysis investigating the link between hyperleukocytosis and false hypoglycemia revealed that out of 126 hypoglycemic events, 34 were classified as false hypoglycemia [27], highlighting the complexity of interpreting blood glucose levels in the context of chemotherapy and the need for vigilant monitoring.

5. Conclusion

In summary, the case of a middle-aged male with small cell lung cancer treated with PEG-rhG-CSF highlights a rare instance of suspected drug-induced pseudohypoglycemia. This event underscores the importance of considering a broad range of factors when assessing blood glucose levels, including the potential impacts of chemotherapy and the treatment's effects on white blood cell proliferation. While pseudohypoglycemia does not require specific intervention, it can complicate the clinical management of blood glucose by mimicking true hypoglycemia. Healthcare providers must remain vigilant in monitoring blood glucose levels, especially in patients undergoing chemotherapy, to ensure accurate diagnosis and timely intervention. Further research is encouraged to elucidate the mechanisms by which treatments like PEG-rhG-CSF may influence glucose metabolism, thereby enhancing clinical guidelines and improving patient care.

Ethics statement

Written consent was obtained.

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Availability of data and materials

All data were included in the article.

Data availability statement

The article contains all data and can be provided upon request.

CRediT authorship contribution statement

Shuya Qi: Writing – original draft. **Lixing Liu:** Writing – review & editing, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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