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| RESEARCH ARTICLE

Metformin: A Common Drug and a Rare Trigger of Hemolytic Reactions

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| ABSTRACT

Metformin-induced hemolytic anemia (MIHA) is a rare adverse effect of the drug metformin, which can cause serious morbidity and result in mortality if not recognized promptly. We present the first MIHA case to be reported in the Kingdom of Bahrain. The case revolves around a 50-year-old male, who was newly diagnosed with diabetes and recently initiated on metformin therapy, presenting to the emergency department with progressive hemolytic anemia. After laboratory investigations ruled out various differentials, a joint decision made by the endocrinologist and hematologist to discontinue metformin led to a notable improvement in symptoms and the complete resolution of the patient's hemolytic anemia.

| KEYWORDS

Metformin; Drug; Hemolytic Reactions

| ARTICLE INFORMATION

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1. Introduction

According to the ADA guidelines, metformin is considered the first-line oral hypoglycemic agent to treat type 2 diabetes mellitus for both the adult and pediatric population above the age of 10 (1). It is prescribed either as a monotherapy or in combination with other drugs when lifestyle modifications have failed to achieve an adequate reduction in blood sugar levels. The most common side effect of metformin is gastrointestinal upset in the form of nausea, vomiting, or diarrhea, affecting up to 30% of patients (2). Other less common side effects include headache, diaphoresis, weakness, rhinitis, and lactic acidosis. Additionally, chronic use of metformin has been associated with vitamin B12 deficiency (3). A minority of patients receiving metformin may experience a sudden clinical onset of hemolysis. We report a case of MIHA, a rare adverse effect caused by the medication.

2. Case

A 50-year-old male presented to the emergency department of Salmaniya Medical Complex on 20/10/2024, complaining of a one-day history of polyuria that was associated with polydipsia, non-specific abdominal pain, and fatigue. The patient denied any other complaints. In terms of past medical history, he has been known to have hypertension, dyslipidemia, and glucose-6-phosphate dehydrogenase (G6PD) deficiency. At the time, he was on amlodipine 5 mg OD, valsartan 160 mg OD, hydrochlorothiazide 12.5 mg OD, rosuvastatin 10 mg OD, and omeprazole 20 mg OD. He also had no known allergies. The physical examination was unremarkable except for mild tachycardia, which was between 100 and 110 beats per minute. A

random blood glucose came back as 21.6 mmol/L (n = 3.9-7.8), hence, he was initiated on hyperglycemic hyperosmolar syndrome (HHS) protocol. The patient was stabilized and was transferred to the medicine ward, where they continuously monitored his glucose levels were continuously monitored via capillary blood glucose. He was diagnosed with type 2 diabetes mellitus after his HbA1c came back as 95 mmol/mol (10.8%). The patient's HHS was resolved, and he was deemed fit for discharge on 27/10/2024. As per the endocrinologist's recommendations, he was started on metformin 500 mg BD. Upon discharge, his hemoglobin (Hb) was 14 g/dL (n = 12-14.5), total bilirubin 11 µmol/L (n = 5-21), and lactate dehydrogenase of 193 U/L (n = 120-246).

On 31/10/2024, the patient presented to the emergency department again, complaining of painless jaundice for a three-day duration, which was associated with mild abdominal pain. The patient denied any symptoms of upper respiratory tract infection, exposure to sick people, or any consumption of fava beans. No melena was reported. The patient was vitally stable, and a physical examination revealed scleral icterus. The abdomen was soft, lax, and non-tender. Labs showed a major drop in hemoglobin to 9.7 g/dL from 14 g/dL when he was discharged a few days back. Moreover, he had a mean cell volume of 84.6 fL (n = 80-100), reticulocyte count of 7.8% (n = 0.5-2.5%), total bilirubin of 60 µmol/L (n = 5-21), indirect bilirubin of 40 µmol/L (n = 3-12), direct bilirubin of 25 µmol/L (n = 0-7), LDH of 269 U/L (n = 125-220), all of which strongly suggested hemolytic anemia. Renal function tests showed urea of 4 mmol/L (n = 2.5-7.5) and creatinine of 75 micromoles/L (n = 60-110). He was transfused with one pack of red blood cells (PRBC) over 4 hours. From there, the patient was admitted to the hematology team and was kept on supportive management with intravenous fluids and folic acid replacement. A full anemia workup was ordered. The labs revealed a G6PD quantitative assay of 150 U/L (males reference range: reduced activity if <600 U/L). A hemoglobin gel electrophoresis revealed a Hb pattern indicative of sickle cell trait, showing an HbA 55.5%, HbA2 3%, HbF 1%, and HbS 33.0%. Folate and B12 levels were both normal, their values being 44.26 nmol/L (n = 7-28) and 523.1 pmol/L (n = 156-672), respectively. Iron studies revealed Iron 14.3 µmol (n = 11.6-31.3), transferrin 2.31 g/L (2.15-3.65), transferrin saturation 24% (15-33), and ferritin 1036.6 µg/L (n = 22-322), ruling out iron deficiency anemia. A stool occult blood test came back negative, and a stool routine microscopy showed no red blood cells. Both direct and indirect Coombs tests returned negative. Peripheral blood collected at admission was not indicative of a specific etiology, showing no schistocytes, bite cells, Heinz bodies, spherocytes, or sickle cells.

While the patient remained on supportive treatment with fluids, his Hb continued to drop to 8.3 g/dL, with his reticulocyte count rising to 10% on 2/1/2024. A Gastrointestinal (GI) review was requested to rule out GI bleeding, but they insisted that the clinical picture is suggestive of hemolytic anemia. On 4/11/2024, his Hb fell to 8 g/dL, and he was transfused with another unit of PRBCs over 3-4 hours. This raised his Hb to 8.9. After a discussion with the endocrinologist, a joint decision between hematology and endocrinology was made to discontinue metformin as it was suspected to be the primary culprit behind the hemolysis. A diagnosis of drug-induced G6PD hemolysis secondary to metformin was made by the hematologist. On 6/11/2024, the patient was found to be clinically and vitally stable. Thus, he was deemed fit for discharge on Lantus 10 units HS, linagliptin 5 mg OD, and folic acid.

The patient followed up at the hematology outpatient clinic on 13/11/2024, a week after his discharge. His follow-up labs showed Hb 10.5 g/dL (compared to 8.9 g/dL on discharge), reticulocyte counts 7% (compared to 9.9% on discharge), and bilirubin 19 µmol/L. Furthermore, his next follow-up appointment revealed an Hb level of 12.6 g/dL, a reticulocyte count of 2.5%, normal liver function tests, and a normal LDH level, conveying a clear improvement in the hemolysis markers. The patient was informed about the resolution of the condition and to attend the emergency department should he experience any new anemia symptoms.

3. Discussion

The case shows a strong temporal relationship between the use of metformin and the development of hemolysis. This is corroborated by the normalization of hemoglobin levels and the hemolytic markers following the cessation of the drug. Although the underlying pathophysiology for metformin-induced hemolysis has not been disclosed, many theories have been postulated. A potential cause is metformin-induced G6PD hemolysis, which was the conclusion reached by both the hematologist and endocrinologist. G6PD is a crucial enzyme that protects RBCs from oxidative damage from reactive oxygen species (4). Its deficiency makes RBCs vulnerable to oxidative stress, and exposure to triggers may lead to hemolytic anemia. The common triggers include the consumption of fava beans, infections, and drugs, especially antimalarials and sulfa drugs, all of which our patient has not been exposed to (5). Metformin has rarely been reported as a trigger for G6PD deficiency-related hemolytic anemia. However, a report by Irshad et al. highlights a case where metformin was implicated in G6PD-related hemolysis in a dose-dependent fashion (6). In this case, a G6PD-deficient patient, who has been on metformin for years, develops hemolysis only after an AKI led to the accumulation of metformin levels. The hemolysis resolved only after dialysis was initiated and metformin levels decreased. About our case, the recent initiation of the drug, along with the absence of AKI, makes it unlikely for metformin to have accumulated sufficiently to trigger G6PD-related hemolysis. Moreover, a peripheral smear did

not reveal findings of G6PD-related hemolysis, such as Heinz bodies or bite cells. Notably, while G6PD levels were low in our patient, the assay should be interpreted cautiously during an acute hemolytic crisis, as it may be falsely elevated or reduced (7–9).

One of the other suggested causes of metformin-induced hemolysis includes drug-induced immune hemolytic anemia (DIIHA). This phenomenon has been associated with multiple drugs, including antimicrobial, anti-inflammatory, and anti-neoplastic drugs (10). However, metformin was only implicated in a paucity of cases. DIIHA can be sub-classified depending on whether the antibodies that form against the red blood cell are drug-dependent or independent (11). Drug-dependent antibodies will only react in the presence of the drug and will form against specific epitopes of the drug or its metabolites or a drug-RBC membrane complex. In contrast, drug-independent antibodies are autoimmune antibodies directed against RBCs that develop regardless of the presence of the culprit drug (12). The way to distinguish between the two is through a direct Coombs test, otherwise known as a direct antiglobulin test. This can reveal if antibodies will react with the RBCs in the presence and the absence of the medication in the patient's serum (13). In our case, the direct Coombs test came back negative, ruling out DIIHA as the pathophysiology behind hemolysis. Other causes of hemolysis, such as hemoglobinopathies, were ruled out by gel electrophoresis.

MIHA is an important cause of hemolysis, which needs to be recognized promptly to prevent catastrophic clinical consequences. A case report published by Packer et al. conveys the potential severity of the disease. It discusses the case of a 56-year-old caucasian, type 2 diabetic, who experienced a drop in Hb from 14.7 g/dl to 6.6 g/dl four days after being started on metformin (14). His labs were also significant for total bilirubin 6.6 mg/dl (direct 2.7 mg/dl), haptoglobin of less than 6 mg/dl, lactate dehydrogenase of 4829 U/l, and a reticulocyte count of 3.51%, along with a positive direct Coombs test, all of which indicated severe hemolysis. The patient's Hb dropped further to 3.3 g/dl, and he became hemodynamically unstable despite blood transfusions. He went into cardiopulmonary arrest and was declared dead 12 hours after admission. The rapid onset of hemolysis after initiation of metformin in this patient supports the temporal relationship between the two.

Apart from this case report, three other cases of MIHA were found in the literature, all of which resulted in recovery (15–17). Interestingly, two of the studies performed a metformin challenge (15,16). This practice involves re-challenging the patient with metformin to determine whether hemolysis will recur. In both studies, the reintroduction of metformin elevated total and unconjugated bilirubin, leading to jaundice. The drug's discontinuation thereafter brought the patients back to baseline clinically and biochemically, supporting the correlation between the use of metformin and hemolysis. With that being said, a metformin rechallenge was not performed in our patient, as his treatment was immediately changed to insulin with linagliptin. There are several limitations to this case report. The nature of the study, being a case report, limits its generalizability and external validity. Although metformin showed the strongest temporal relationship with the onset and resolution of the hemolytic event, there was no laboratory report or objective value that confirms that it is the actual trigger. Additionally, a metformin challenge was not performed to confirm the causality between the drug and hemolysis. This could have strengthened the evidence to support metformin's role in the onset of hemolysis. A longer follow-up period may have also helped ensure that a hemolytic event was less likely to occur in the absence of metformin.

The study highlights the cruciality of recognizing metformin-induced hemolytic anemia as a rare side-effect of the drug metformin. Even though simply discontinuing the drug may lead to rapid improvement, failure to recognize the drug as the culprit behind the hemolysis can lead to detrimental outcomes and possibly death.

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References

[1] Corcoran C, Jacobs TF. Metformin. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025.
[2] Nabrdalik K, Skonieczna-Żydecka K, Irlik K, Hendel M, Kwiendacz H, Łoniewski I, et al. Gastrointestinal adverse events of metformin treatment in patients with type 2 diabetes mellitus: A systematic review, meta-analysis and meta-regression of randomized controlled trials. Front Endocrinol (Lausanne). 2022 Sep 14;13:975912.
[3] Kirkiz S, Yarali N, Arman Bilir O, Tunc B. Metformin-induced hemolytic anemia. Med Princ Pract. 2014;23(2):183–5.
[4] Richardson SR, O'Malley GF. Glucose-6-phosphate dehydrogenase deficiency. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025.
[5] Glucose-6-phosphate Dehydrogenase Deficiency: A Review [Internet]. [cited 2025 Feb 23]. Available from: https://ijms.info/IJMS/article/view/637/1124

[6] Irshad Y, Nadeem M, Khan U, Tariq E, Khakwani A. Case Report: Hemolysis in a G6PD-deficient patient, a dose-dependent effect of metformin. F1000Res. 2020 Oct 14;9(1234):1234.
[7] Eziokwu AS, Angelini D. New diagnosis of G6PD deficiency presenting as severe rhabdomyolysis. Cureus. 2018 Mar 28;10(3):e2387.
[8] Minucci A, Giardina B, Zuppi C, Capoluongo E. Glucose-6-phosphate dehydrogenase laboratory assay: How, when, and why? IUBMB Life. 2009 Jan;61(1):27–34.
[9] Khan U, Hadid T. RUSH for G6PD! [Internet]. [cited 2025 Feb 23]. Available from: https://imagebank.hematology.org/image/60937/rush-for-g6pd?utm_source=chatgpt.com
[10] Garratty G. Drug-induced immune hemolytic anemia. Hematology Am Soc Hematol Educ Program. 2009;2009(1):73–9.
[11] Arndt PA, Garratty G. The changing spectrum of drug-induced immune hemolytic anemia. Semin Hematol. 2005 Jul;42(3):137–44.
[12] Hansen DL, Frederiksen H. A leap in recognizing drug-induced immune hemolytic anemia. Blood Adv. 2024 Feb 13;8(3):815–6.
[13] Arndt P, Garratty G, Isaak E, Bolger M, Lu Q. Positive direct and indirect antiglobulin tests associated with oxaliplatin can be due to drug antibody and/or drug-induced nonimmunologic protein adsorption. Transfusion. 2009 Apr;49(4):711–8.
[14] Packer CD, Hornick TR, Augustine SA. Fatal hemolytic anemia associated with metformin: a case report. J Med Case Rep. 2008 Sep 10;2(1):300.
[15] Lin KD, Lin JD, Juang JH. Metformin-induced hemolysis with jaundice. N Engl J Med. 1998 Dec 17;339(25):1860–1.
[16] Kashyap AS, Kashyap S. Haemolytic anemia due to metformin. Postgrad Med J. 2000 Feb;76(892):125–6.
[17] Meir A, Kleinman Y, Rund D, Da'as N. Metformin-induced hemolytic anemia in a patient with glucose-6- phosphate dehydrogenase deficiency. Diabetes Care. 2003 Mar;26(3):956–7.