CASE REPORT

Case Report: Hemolysis in a G6PD-deficient patient, a dose-dependent effect of metformin [version 1; peer review: 1 approved, 1 approved with reservations]

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Abstract

Glucose-6-phosphate deficiency is an X-linked genetic disorder, which predisposes erythrocytes to oxidative stress, resulting in hemolysis. It is the most common enzymatic deficiency, and typically affects African, Asian, Mediterranean, and Middle Eastern lineages. It can be induced by some medications, chemicals, and foods. Metformin is an uncommon drug to cause hemolysis in G6PD-deficient patients.

We report a case of a 52-year old African American male with G6PD-related hemolysis secondary to toxic metformin accumulation with acute kidney injury (AKI). The patient was a type-2 diabetic and was taking metformin (500mg twice daily) for three years. He presented to the ER with nausea, vomiting, and diarrhea for last three days with severe hemodynamic instability. Labs revealed hemoglobin 15mg/dl, white blood count 28 mm³/L, creatinine 10 mg/dl, blood urea nitrogen 100 mg/dl, bicarbonate 7 mEq/L, lactic acid 17 mg/dl, pH 6.8, pCO₂ 21mmHg, metformin 41 mcg/ml, albumin-globulin 41. Severe sepsis protocol was activated; IV fluids 30ml/kg bolus and antibiotics were given. CT abdomen revealed colitis. The patient was started on continuous renal replacement therapy. The next day, the patient's hemoglobin dropped to 12.6 mg/dl. A hemolytic panel was unswerving with hemolysis and G6PD levels reported low at 1.72. The patient improved with antibiotics, but the hemolysis continued. Metformin toxicity induced hemolysis was suspected. The patient's hemoglobin dropped to 6g/dl and he received blood transfusions. His hemoglobin started to improve with hemodialysis sessions, as metformin levels started to normalize, emphasizing the fact that patient was clearing metformin.

Unlike most cases reported, in which hemolysis occurs within days to months of starting metformin, in our patient it occurred due to the

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1. Carmelo J Blanquicett , Moffitt Cancer Center, Tampa, USA 2. Shaimaa El-Ashwah , Mansoura University, Mansoura, Egypt		
Any reports and responses or comments on the article can be found at the end of the article.		

cumulative effect of metformin because of the patient's underlying AKI. This led us to propose that the hemolytic effect of metformin may not only be time-dependent but also dose-dependent.

Keywords

metformin, glucose-6-phosphate dehydrogenase deficiency, hemolytic anemia, acute kidney injury.

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Introduction

G6PD is an X-linked inherited red blood cell enzymatic disorder and affects 400 million individuals worldwide. It is most frequently seen in individuals with African, Asian, Mediterranean, or Middle Eastern lineage. The disorder can be asymptomatic but varied gene mutations cause different levels of enzyme deficiency, leading to inconstant disease presentation¹. The deficiency causes neonatal hyperbilirubinemia, acute hemolysis, and chronic hemolysis. Acute hemolysis occurs due to exposure to an oxidative stressor that can be in the form of an infection, oxidative drug, or fava bean.

Numerous medications have been identified to induce G6PD deficiency induced hemolysis, but metformin is seldom reported as a cause of hemolysis. It is an oral antidiabetic drug and the first-line agent in the treatment of type II diabetes mellitus. Its side effects include lactic acidosis, a serious condition that occurs in case of drug overdose (most commonly seen in patients with liver disease and kidney disease), individuals with low circulating oxygen level in the blood (e.g., congestive heart failure, recent stroke), alcoholism, and dehydration². Hemolysis is not a side effect of the drug. So far only eight cases have been reported^{3–10} in the literature where metformin use resulted in either G6PD associated hemolysis^{4,6} or drug-induced hemolysis^{3,5,7–10}.

Case presentation

A 52-year-old African American male with significant past medical history of type II diabetes mellitus, hypertension, presented to the ER with complaints of severe vomiting, nausea, and diarrhea for three days. The patient was taking losartan (50 mg per oral daily) and metformin (500mg twice daily) for the last three years. He was compliant with his medications despite having profuse diarrhea for the last 3–4 days. On examination, the patient was severely hypovolemic and hemodynamically unstable with blood pressure of 76/46 mm of hg.

The patient was admitted and managed with IV fluids and meropenem 1gm iv BID, as per severe sepsis guidelines.

Initial investigations revealed the following labs: hemoglobin 15mg/dl (normal range, 11.9–14.8mg/dl); white blood count 28 mm³/L (3.8–10.4mm³/L); creatinine 16.77 mg/dl (0.70–1.30mg/dl); blood urea nitrogen 100 mg/dl (8–20mg/dl); potassium 5mmol/L (3.5–5mmol/L); blood glucose 78mg/dL (140–200mg/dL); bicarbonate 7 mmol/L (23–28mmol/L); lactic acid 17 mg/dl (6–19mg/dl); arterial blood gas showed severe metabolic acidosis; pH 6.8 (7.38–7.44); pCO₂ 21mmHg (38–42mmHg); metformin level was 41; and anion gap 41mmol/L (7–13mmol/L). Diagnosis of sepsis and metformin-induced severe lactic acidosis was suspected.

A CT abdomen/pelvis was done, which showed colitis with some diverticulitis. Blood cultures were sent, and the patient was started on meropenem 1 gram, intravenous twice daily, empirically. The patient was emergently started on continuous renal replacement therapy in the light of severe metabolic and lactic acidosis. The next day, the patient developed jaundice, and hemoglobin dropped from 15 to 12.6 mg/dl. Total bilirubin was 3.2mg/dl (0.3–1mg/dl) and indirect bilirubin was 2.5mg/dl (0.2–0.7mg/dl). A hemolytic panel was consistent with hemolysis, and G6PD levels were reported as low at 2.82 (5–15 units/g of hemoglobin). Antiglobulin tests for IgG and C3 were negative with normal C3 and C4 levels. HIV ELISA and Reichlin's profile was negative.

The patient markedly improved clinically two days' post-admission with IV antibiotics, emergent hemodialysis with the resolution of sepsis, but the hemolysis persevered and anemia deteriorated. Metformin toxicity induced hemolysis was suspected after reviewing the literature. The patient dropped hemoglobin to the nadir of 6 g/dl on day five of admission with hematocrit dropping to 15%. He underwent packed red blood transfusion considering life threatening low hematocrit and hemoglobin levels. The patient's hemoglobin levels improved with intermittent hemodialysis as the metformin levels normalized, emphasizing the fact that the patient was clearing metformin from the system. Table 1 shows the downward trend in the metabolic profile of the patient.

Table 1. Metabolic profile of the patient showing downward trend.

Indices	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Red blood cells (M/cmm)	3.08	2.53	2.42	2.32	2.29	2.06	1.87
Hemoglobin (g/dl)	15	12.6	9.3	7.7	7.0	6.5	6.0
Total bilirubin (mg/dl)	3.2	2.7	2.4	2.3	2.4	2.4	2.4
Creatinine (mg/dl)	10.0	7.9	8.7	9.1	7.3	5.2	3.4
Lactic acidosis (mmol/dl)	17	15.0	7.9	2.1	1.1	1.0	1.0
Hematocrit (%)	48	36	28.3	22.4	21.3	19.4	17.6
Platelets (K/cmm)	160	166	171	173	207	276	347

The patient was discharged home on day 11 once his hemoglobin rose to 9.8g/dl and creatinine dropped back to 1.4mg/dl. He remained uneventful after the dialysis. Metformin use was prohibited for the rest of life. In our patient, metformin-induced hemolysis occurred due to dose-dependent toxicity, as previously he was using metformin 1 gram per oral twice daily but developed no side effects.

Discussion

Our patient's medication history was meticulously studied in order to find any other drug causing hemolytic anemia besides metformin. No other hemolytic risk factors were identified in the patient's medical history. His blood G6PD levels were reported significantly low at 1.72. The drop in hemoglobin did not improve even with the cessation of antibiotics and dropped consistently until metformin was cleared from the patient's system by dialysis, confirming that it was a dose-dependent effect of metformin. Our patient had acute kidney injury secondary to sepsis, gastroenteritis and hypovolemia and unfortunately the patient continued to take his metformin during this phase, which resulted in accrual of the metformin levels.

A literature search was performed concerning the side effects of metformin and its connection with G6PD related hemolytic anemia. Metformin-induced hemolysis in G6PD patients is very rare and, to the best of our knowledge, only seven cases are reported in the literature³⁻¹⁰. Discontinuation of metformin resulted in the recovery of most cases, except one which had a fatal outcome (hemoglobin drop of 11.4mg/dl) regardless of metformin discontinuation⁵. That patient developed fulminant and fatal Coombs-positive hemolytic anemia, which was temporally related to the initiation of metformin treatment in the absence of any other likely cause.

Table 2 describes the demographic variation of individuals and the temporal relationship after the initiation of metformin and the onset of hemolytic anemia from the literature. All the patients developed hemolytic anemia irrespective of the dosage of metformin, but in one patient a definitively higher dosage caused the sudden onset of hemolytic anemia within hours of metformin toxicity secondary to overdosing (45000mg)⁹ with a drop in hemoglobin of 8.6g/dl. This patient also developed lactic acidosis and underwent continuous renal replacement therapy. In our patient, due to acute kidney injury, hemolytic anemia started after a day with a severe drop in hemoglobin of 9.5g/dl over a course of four days. Hemolysis occurred due to the cumulative effect of metformin because

of the patient's underlying acute kidney injury. Naranjo's adverse score was 5. This leads us to propose that the hemolytic effect of metformin may not only be time-dependent but also dose-dependent. Both of these cases prove that with higher doses and renal impairment (as in our case), the drastic effect of metformin-induced hemolysis was seen together with lactic acidosis.

From the literature, it can be observed that most patients developed hemolytic anemia within 2–14 days of metformin commencement. Our patient is unique as he developed anemia in his third year of treatment after accumulating toxic level of metformin in the setting of acute kidney injury and lactic acidosis. Patients with North African, Jewish descent had low G6PD activity with a negative anti-globin test, showing the connection between G6PD-induced hemolytic anemia secondary to the use of metformin as seen in two cases prior in addition to our case^{4,6}. Other cases with positive antiglobulin test^{3,5,7} increased the possibility of drug-induced hemolytic anemia secondary to antibody formation. Supportive treatment was given in all cases, except in the case of metformin poisoning⁹ and our case, which required continuous renal replacement therapy and blood transfusion. The case with the fatal outcome⁵ developed cardiac arrest after treatment under advanced cardiac life support protocol.

Conclusion

Metformin induced hemolysis is an infrequent presentation of hemolytic anemia. Patients with G6PD deficiency can be more predisposed to this side effect, and this should always be kept in the back of mind while reconnoitering causes of hemolysis in G6PD deficiency. Clinicians should be vigilant before starting metformin and renal function test should be periodically done to rule out any acute kidney injury as it triggers the toxic effects of metformin, leading to severe adverse effects like lactic acidosis and hemolysis. Patients should be educated that in case of weakness, pallor, fatigue, and jaundice, they should report to hospital immediately.

The temporal relationship has been beforehand observed in metformin-induced hemolysis, but the dose-dependent snowballing effect can also give a similar presentation of metformin toxicity. Metformin induced hemolysis could be either due to drug-induced antibodies with normal G6PD levels or by oxidative damage in G6PD deficient individuals with normal or low G6PD levels.

Table 2. Previous case reports reporting metformin-induced hemolysis.

First author	Age	Gender	Ethnicity	Total daily dose of metformin in mg	Increase in T.B from baseline	Decrease in Hb from baseline	Time from metformin initiation to onset of symptoms	Direst anti-globin test	G6PD activity	Treatment	Outcome
Kirkiz <i>et al.</i> ³	17	Male	Unknown	250	N/A	1.4g/dl	2d	IgG +, C3-	Normal	Supportive	Recovery
Blum <i>et al.</i> ⁵	29	Male	North African Jewish	2550	N/A	0.7g/dl	14d	Negative	Low	Supportive	Recovery
Packer <i>et al.</i> ⁴	56	Male	Caucasian	1000	6.1mg/dl	11.4g/dl	2d	IgG+, C3-	N/A	Blood transfusion and ACLSP	Fatal
Meir <i>et al.</i> ⁶	68	Female	North African Jewish	2550	N/A	4g/dl	14d	Negative	Low	Supportive	Recovery
Kashyap <i>et al.</i> ⁷	51	Female	Unknown	1700	N/A	N/A	9d	IgG-, C3+	Normal	Supportive	Recovery
Lin <i>et al.</i> ⁸	46	Male	Unknown	2500	5.3mg/dl	N/A	10d	Unclear	N/A	Supportive	Recovery
Jagia <i>et al.</i> ⁹	36	Male	Unknown	45000	N/A	8.6g/dl	Hours	Negative	Normal	CRRT and BT	Recovery
Nichole <i>et al.</i> ¹⁰	53	Male	Caucasian	1000	2.8mg/dl	1.8g/dl	24 hours	Not obtained	Low	Supportive	Recovery
Our case	52	Male	African American	1000	4mg/dl	9.5g/dl	24 hours after AKI	Negative	Low	CRRT and BT	Recovery

ACLSP, advanced cardiac life support protocol; BT, blood transfusion; CRRT, Continuous Renal Replacement Therapy; Hb, hemoglobin; T.B, total bilirubin

Consent

Written informed consent for publication of the case report along with any associated images was obtained from the patient.

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

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Shaimaa El-Ashwah

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Interesting case report concerning argue of dose-dependent toxicity especially that the patient was on the same dose for 3 years, however, is there a possibility that infection and dehydration could be risk factors for lactic acidosis and hemolysis?

- It would be better to determine the G6PD variant
- Was there a nephrology consultation concerning AKI? is this AKI on top of CKD as there is a history of HTN and DM?
- Double check values written in abstract & case description and also, units used.
- Patient's management by IV fluids and antibiotics was repeated twice in the case description

Is the background of the case's history and progression described in sufficient detail?

Partly

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Haematology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 07 December 2020

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Carmelo J Blanquicett

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The case report highlights a previously-described, but rare occurrence. It would be interesting to determine whether the g6pd variant of the patient was investigated. Was it? Was nephrology consulted to investigate the AKI? Overall, interesting phenomenon is presented, particularly the argument of dose-dependance that occurred due to lack of drug clearance as a result of AKI; however, details of the AKI investigation/workup would be useful to know (UA and microscopy results. etc).

Is the background of the case's history and progression described in sufficient detail?

Yes

Are enough details provided of any physical examination and diagnostic tests, treatment given and outcomes?

Partly

Is sufficient discussion included of the importance of the findings and their relevance to future understanding of disease processes, diagnosis or treatment?

Yes

Is the case presented with sufficient detail to be useful for other practitioners?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: IM/heme/onc

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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