Case Report

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Glucose 6 Phosphate Dehydrogenase Deficiency Unmasked by Diabetic Ketoacidosis: An Underrated Phenomenon

Hematology Section

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ABSTRACT

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked disease responsible for moderate to severe hemolytic anaemia. Despite being the most common erythrocyte enzyme disorder, it is often overlooked in the regular diagnostic parlance. A 40-year-old male patient admitted to the casualty with an acutely exacerbated diabetic ketoacidosis, showed features of hemolytic anaemia on peripheral smear examination. Crucially, the spherocytes and bite cells suggested a possibility of G6PD deficiency. This was substantiated by an increased reticulocyte count (6.8%) and a reduced quantitative G6PD enzyme assay (7.2%). There was no significant family or prior medical/drug history. Interestingly, the hemolytic features were evidenced when blood glucose levels were returning to normal values. The insulin mediated NADPH loss may have resulted in an increased erythrocyte oxidant sensitivity and a loss of sulfhydryl group availability; causing hemolysis to manifest. G6PD deficiency is conventionally affiliated with drug induced oxidative stress. But an association with a diabetes mellitus is seldom reported. This case is being presented as it highlights the lesser known complication of diabetic crisis such as hemolysis secondary to a G6PD deficiency.

Keywords: G6PD deficiency, hemolysis, blister cells, diabetic ketoacidosis

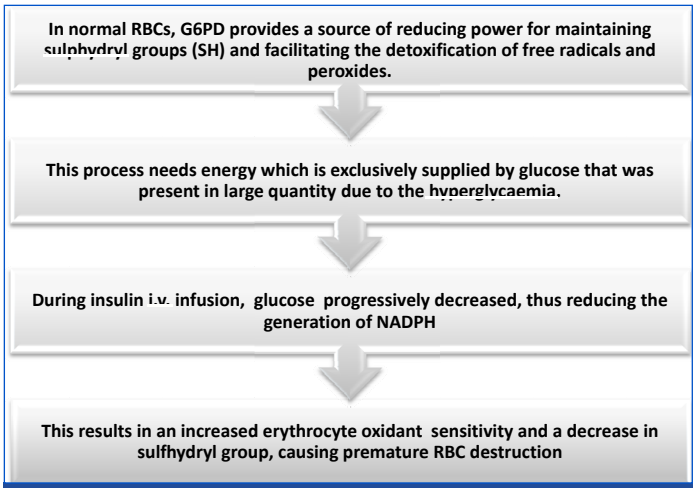
INTRODUCTION

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked disease responsible for moderate to severe hemolytic anaemia. Hemolysis is usually associated with the ingestion of fava beans or drugs such as sulphonamides, anti-malarials etc. Hemolytic anaemia in diabetics has conventionally been associated with bacterial infections and hemolytic drugs. But hemolysis due to G6PD deficiency in patients with diabetic ketoacidosis (DKA) has seldom been reported. This case report aims at highlighting the lesser known, yet an important complication of DKA.

CASE REPORT

A 40–year–old male was brought to the casualty at Kasturba Hospital, Manipal, India in a semiconscious state with low grade fever. He also had a non-healing ulcer on the sole of the left foot. He was a known case of diabetes mellitus, on treatment since the past 15 years. He was on insulin injections, but was apparently irregular since the couple of years. On examination, the pulse rate was 116/min; rapid and thready but regular, Respiratory rate was 38/min, shallow and the accessory muscles were being used actively. The patient was responding to commands. No organomegaly/lymph nodes were appreciated. Additional work-up such as ECG, ECHO, ultrasound scan of the abdomen was normal. On motor examination, weakness in lower limb (grade 3/5) was recorded. CNS examination-slurred speech and poor eye opening was noted. Glasgow Coma Score was 10/15. Based on the clinical and laboratory data, a diagnosis of diabetic ketoacidosis was made. Intravenous insulin infusion was initiated along with, fluid support and broad spectrum antibiotics.The laboratory investigations done on admission were as follows: RBC: 2.14 million/ cu.mm. The haemoglobin was reduced (8.19g/dL). The total leucocyte count was increased (16,400 cu.mm) showing a neutrophilic count with left shift. However, no toxic granules were seen. The platelet count was reduced (60,000/cu.mm). The biochemistry parameters were also deranged with an elevated random blood sugar (526mg%). The liver function tests were unremarkable except for amildy elevated transaminases. The renal function tests were deranged with elevated urea (87mg%) and creatinine (2.3mg%). Plasma osmolality was increased (404mmol/L) and urine dipstick was positive was positive for protein, sugar and ketone bodies.

The peripheral smear showed sparse RBC distribution with a normocytic normochromic anaemia. The smear also showed striking poikilocytes such as spherocytes, nucleated RBCs and fragmented cells, including “bite” cells [Table/Fig-1]. The reticulocyte count was elevated 6.8%. In view of the above findings, we offered a diagnosis of hemolytic anaemia, possibly secondary to infection and a work-up for the same. The D–dimer assay was mildly elevated (6.4); but not diagnostic of a full-blown hemolysis. Both direct and indirect



[Table/Fig-1]: Pathogenesis of hemolysis of RBCs in case of diabetic ketoacidosis

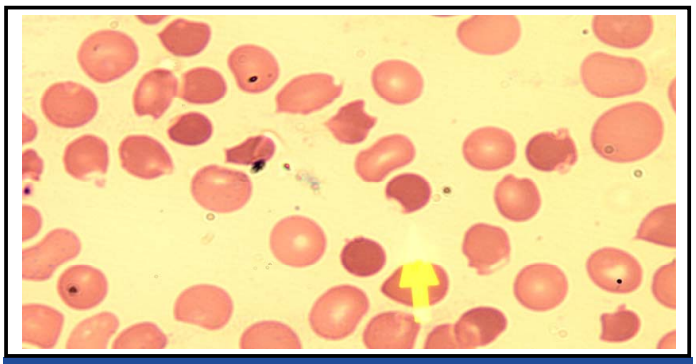
Coomb’stest were negative. The blood culture was sterile. We continued to see the hemolytic picture in the smear for 3 subsequent days.

Hence, we requested a G6PD assay to rule out a G6PD deficiency. The spectrophotometric assay showed a mildly reduced level of the enzyme: 7.2% (normal range: 8-18%). Based on the laboratory parameters and RBC morphology, we offered a diagnosis of a mild G6PD deficiency secondary to diabetic ketoacidosis. We requested the clinician to assess for family history of G6PD deficiency. Since

the patient lacked a family and drug history, we concluded that the hemolysis was secondary to G6PD deficiency.

DISCUSSION

Diabetes mellitus and its associated complications span a myriad of events which are well celebrated in literature.Glucose-6-phosphate dehydrogenase (G6PD) deficiency manifesting in such a wide-spread disease is however unheard of.While acute metabolic complications such as diabetic ketoacidosis (DKA) are known to be precipitated by stress, the same fundamentals could be implicated in the hemolysis of the RBCs.The existential evidence of G6PD deficiency in DKA has been reported since 1984 (Shalev et al.,) [1]. Eversince, sporadic case reports have appeared in literature highlighting the unusual and under-reported nature of this phenomenon. In a G6PD-deficient subject, hemolysis may occur as a result of ingestion of various drugs, ingestion of specific food substances and commonly, infection. None of the above-mentioned history could be detailed



[Table/Fig-2]: Peripheral smear showing anaemia with spherocytes and mild poly-chromasia. Note the bite cells (arrow) (Leishman; x200)

in our case.Though this X-linked disease is known to affect males exclusively, Errico et al., [2] have described it in females as well. It is hypothesized that blood glucose normalization during DKA treatment produced a stressing glucose deprivation for the energy-dependent function of the red blood cells causing premature RBC destruction [2]. The proposed hypothesis [2,1] for the hemolysis is depicted in [Table/Fig-2].

In our case, the patient could have been mildly G6PD deficient. This possibility could not be confirmed as the patient had no significant family or medical history. A metabolic crises such as DKA could have unmasked this deficiency. Generally, diabetics are more prone to develop infections, which, over the years have been frequently incriminated for hemolytic anaemia [Table/Fig-2]. In the present case, the work-up for infections was negative. Some other causes of G6PD deficiency in diabetic subjects could be because of hypoglycaemia [1], ketoacidosis in the African [3,4], but not Mediterranean variant of G6PD [5], and following administration of metformin [6] or glibenclamide [7]. In the present case, the patient was not on any oral hypoglycemic medication. The other possibilities are also ruled out as the laboratory investigations did not correlate with them. It has been observed that defects in the G6PD gene correlate with diabetes and a more recent study proposed that alterations in genes controlling both insulin secretion and G6PD-mediated antioxidant defences may contribute to a predisposition to diabetes [8]. Diabetic patients who develop hemolysis during DKA treatment rarely need blood transfusions. The new red blood cells, grown in a normal glycemic medium, find a physiologic source of energy for generating a sufficient quantity of NADPH [9].

CONCLUSION

Hemolytic anaemias observed in a background of diabetes mellitus are generally attributed to infections or drugs. A finding of spherocytes and bite cells in a setting of DKA is usually attributed to drugs or infections.in the absence of the above, a possibility of G6PD deficiency should be considered; especially when the plasma glucose level is on the decline.This case highlights the lesser known complications of diabetic crisis such as hemolysis secondary to a G6PD deficiency, which can be overlooked.

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