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Case Report

Uncovering the Surreptitious Mystery of Chronic Hemolysis: A Rare Case Report

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Abstract: DyGlucose-6-phosphate dehydrogenase (G6PD) deficiency is the most common human enzymopathy, yet its diagnosis is frequently overlooked in adults with unexplained chronic hemolysis. We report a 52-year-old male who presented with bilateral lower limb swelling, fatigue, and exertional dyspnea. Laboratory evaluation revealed severe anemia (hemoglobin 2.9 g/dL), pancytopenia, elevated lactate dehydrogenase, indirect hyperbilirubinemia, reticulocytosis, and reduced G6PD activity (6.53 U/g Hb). Peripheral blood smear demonstrated microcytic hypochromic red cells, anisopoikilocytosis, bite cells, and Heinz bodies on supravital staining. Bone marrow examination showed erythroid hyperplasia with megaloblastic changes, and ultrasound confirmed hepatosplenomegaly. The patient had a history of recurrent hemolytic episodes requiring transfusions, but no definitive etiology had been established previously. He was managed with packed red blood cell transfusions and folic acid supplementation, leading to clinical and hematological improvement. This case underscores the importance of considering G6PD deficiency in any adult with recurrent hemolytic anemia, even in the absence of an obvious oxidative trigger. Early recognition and avoidance of oxidative stressors are essential to prevent complications and improve outcomes.

Keywords: G6PD deficiency, hemolysis, erythroid hyperplasia, bite cells, Heinz bodies, oxidative stress.

INTRODUCTION

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is an X-linked enzymatic disorder that affects more than 400 million individuals worldwide [5]. The G6PD enzyme catalyzes the first step of the hexose monophosphate shunt, generating nicotinamide adenine dinucleotide phosphate (NADPH), which is critical for protecting red blood cells from oxidative damage [4]. Deficiency of this enzyme renders erythrocytes vulnerable to hemolysis under conditions of oxidative stress, such as infections, certain medications, or ingestion of fava beans [6]. The clinical spectrum of G6PD deficiency ranges from asymptomatic states to acute hemolytic episodes, neonatal jaundice, and rarely chronic non-spherocytic hemolytic anemia [6]. While classically considered a disease of childhood, it can present for the first time in adulthood, often mimicking other causes of hemolytic anemia. Diagnosis relies on a high index of suspicion, characteristic peripheral blood findings (bite cells, Heinz bodies), and quantitative G6PD assay [4]. However, diagnosis may be confounded during acute hemolysis because reticulocytes have higher enzyme activity and can produce falsely normal results [6]. We report a case of an adult male with recurrent unexplained hemolytic anemia who was ultimately diagnosed with G6PD deficiency, highlighting the diagnostic challenges and the importance of systematic evaluation.

CASE PRESENTATION

A 52-year-old male presented to the general medicine outpatient department with complaints of bilateral lower limb swelling for one month, accompanied by facial puffiness, generalized fatigue, and shortness of breath on exertion

(Modified Medical Research Council grade 3). He had been taking over-the-counter anti-inflammatory medications for joint pain, but the specific agent and duration were unclear.

His medical history was significant for similar episodes in the past, for which he had required packed red blood cell transfusions. Previous laboratory investigations (Table 1) revealed severe anemia (hemoglobin 2.9 g/dL), pancytopenia, markedly elevated lactate dehydrogenase (1331 U/L), and indirect hyperbilirubinemia. Bone marrow aspiration at that time had shown erythroid hyperplasia with megaloblastic changes, but no definitive diagnosis was established. The patient had no known family history of hematological disorders and no history of neonatal jaundice.

On physical examination, he appeared pale and had bilateral pitting pedal edema. Cardiovascular examination revealed a soft systolic murmur best heard over the pulmonary area. Abdominal examination demonstrated mild hepatosplenomegaly; no lymphadenopathy was noted.

Table-1 Previous Laboratory Investigations of the patient.

Parameter	Result	Normal range
Hemoglobin (g/dL)	2.9	12-17
Hematocrit(PCV) %	9.7	40-50
RBC count(million/cumm)	1.07	4.5-5.5
ESR(mm)	110	5 -15
Total leucocyte count (x10^9/L)	1.8	4-10
Platelet count (x10^3/cumm)	112	150-140
LDH (U/L)	1331	207-414
Total bilirubin (mg/dL)	1.2	0.3-1.1
Direct bilirubin (mg/dL)	0.7	0-0.2
Peripheral Smear- Pancytopenia.		
Bone Marrow Aspiration Study-Erythroid hyperplasia with megaloblastic changes.		

Table 2: Present Laboratory investigations of the patient

Parameter	Result	Normal range
Hemoglobin (g/dL)	5.7	12-17
Hematocrit (PCV) %	12.7	40-50
RBC count(million/cumm)	1.63	4.5-5.5
MCV (fl)	77.9	83-101
MCH (pg)	20.8	27-32
MCHC %	26.8	31.5-34.5
RDW (CV%)	23.3	11-16
RDW SD (fl)	63.3	35-56
Total leucocyte count (x109/L)	2.78	4-10

Neutrophils	56.5	20-80
Lymphocytes	32.9	22-44
Monocytes	9.7	2-10
Eosinophils	0.6	1-4
Basophils	0.3	<1
Absolute neutrophil count (x109/L)	1.57	2-7
Absolute lymphocyte count (x109/L)	0.91	1-3
Reticulocyte count	4.2	0.5-2.5
Platelet count (x103/cumm)	112	150-140
Glucose 6 phosphate dehydrogenase-Quantitative (U/g Hb)	6.53	8.6 – 18.6

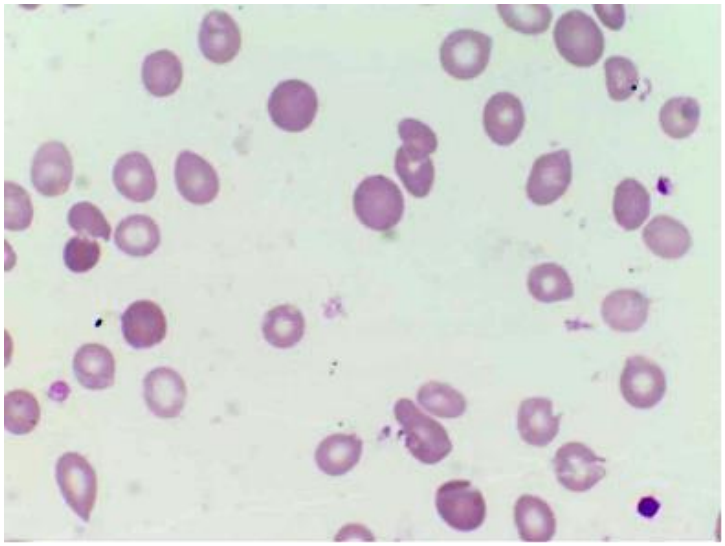

FIGURE 1: (100X) peripheral smear showing microcytic hypochromic rbc's, anisopoikilocytosis with microspherocytes.

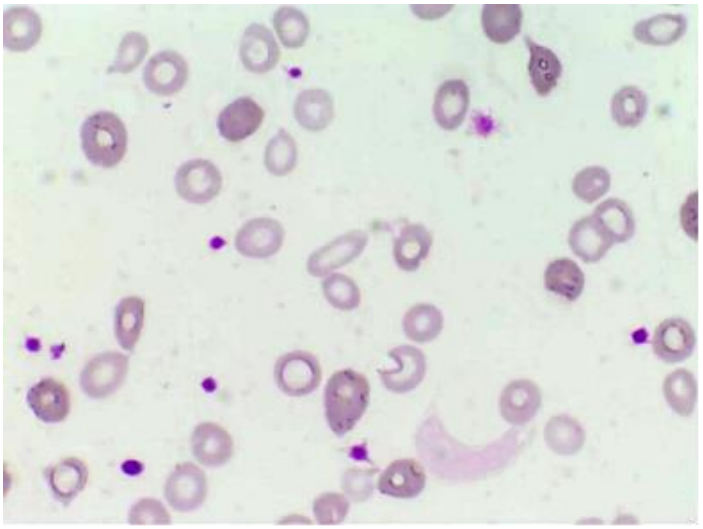

FIGURE 2: (100X) peripheral smear showing bite cells.

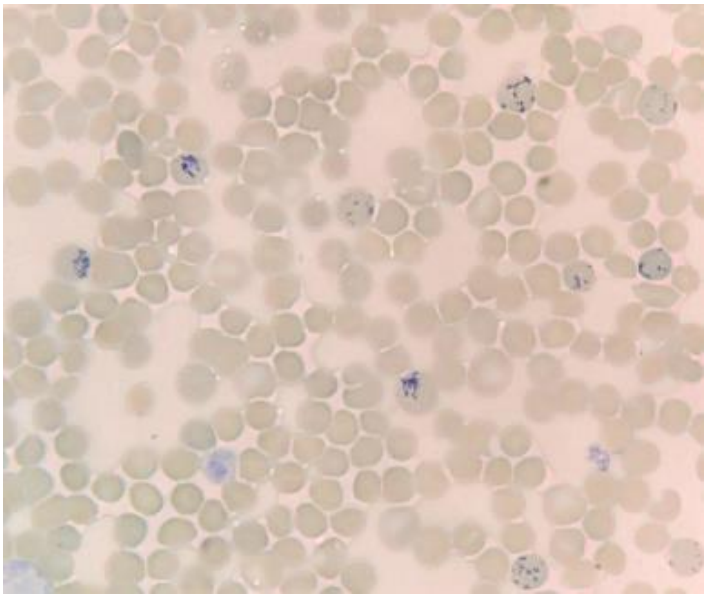

FIGURE 3 :(40X) Supravital stain showing increased reticulocyte count.

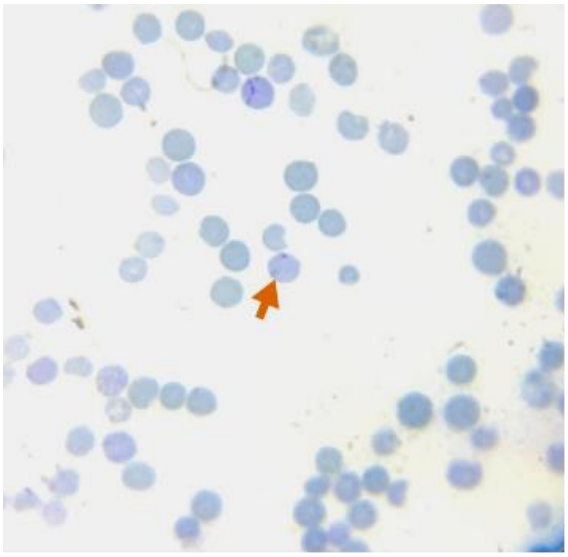

FIGURE 4: (100 X) supravital stain showing Heinz bodies marked by arrow.

Laboratory investigations (Table 2), showed persistent anemia (hemoglobin 5.7 g/dL) with microcytic hypochromic indices (MCV 77.9 fL, MCH 20.8 pg, MCHC 26.8%), an elevated red cell distribution width (RDW-CV 23.3%), and reticulocytosis (4.2%). Leukopenia (total leucocyte count 2.78 × 10^9/L) and thrombocytopenia (platelets 112 × 10^3/µL) were again noted. Hemolysis markers were consistent with active hemolysis: lactate dehydrogenase was elevated (not repeated in Table 2 but previously 1331 U/L) and total bilirubin was 1.2 mg/dL with direct fraction 0.7 mg/dL. Quantitative G6PD assay measured 6.53 U/g Hb (reference range 8.6–18.6 U/g Hb), confirming deficiency.

Peripheral blood smear examination (Figure 1 and 2) revealed erythropenia, microcytic hypochromic red blood cells with severe anisopoikilocytosis, elongated cells, microspherocytes, fragmented cells, polychromatophils, occasional bite cells, and nucleated red blood cells. Supravital staining (Figure 3 and 4) demonstrated an increased reticulocyte count and prominent Heinz bodies.

Ultrasound of the abdomen confirmed hepatosplenomegaly with mild ascites. The constellation of recurrent hemolytic episodes, bite cells, Heinz bodies, reticulocytosis, and reduced G6PD activity led to the diagnosis of G6PD deficiency-associated hemolytic anemia. The patient was treated with two units of packed red blood cells and oral folic acid supplementation (5 mg daily). His symptoms improved, and repeat hemoglobin rose to 9.2 g/dL with normalization of leukocyte and platelet counts by the time of discharge. He was counseled to avoid oxidative

stressors, including NSAIDs and fava beans, and provided with a list of medications contraindicated in G6PD deficiency.

DISCUSSION

Hemolytic anemia results from premature destruction of red blood cells and can be classified as acute or chronic, inherited or acquired, and intracorpuscular or extracorpuscular [1,3]. Intracorpuscular defects include membranopathies, enzymopathies, and hemoglobinopathies; among enzymopathies, G6PD deficiency is the most prevalent [3,5]. This case illustrates several key aspects of G6PD deficiency that merit discussion: the diagnostic pitfalls in adults, the morphological clues on peripheral smear, the significance of bone marrow findings, and the principles of management.

Diagnostic challenges in adults.

Although G6PD deficiency is an X-linked condition typically manifesting in males, it can present for the first time in adulthood, often provoked by an oxidative trigger [5,6]. Our patient had recurrent hemolytic episodes over an unspecified period, yet the diagnosis was not made until this admission. This delay is not uncommon; physicians may not consider G6PD deficiency in older adults without a prior history or family history. Furthermore, during acute hemolysis, G6PD levels may be falsely normal because young erythrocytes (reticulocytes) have higher enzyme activity [6]. In our case, the G6PD level was unequivocally low (6.53 U/g Hb) despite reticulocytosis (4.2%), confirming the diagnosis. When suspicion is high and initial testing is normal, repeat testing several weeks after recovery is recommended [4].

Peripheral blood smear as a diagnostic cornerstone.

The peripheral smear in G6PD deficiency during hemolytic crises is characterized by "bite cells" (blister cells) – erythrocytes from which Heinz bodies have been pitted by the spleen – as well as spherocytes, fragmented cells, and polychromasia [6]. Heinz bodies, aggregates of denatured hemoglobin, are not visible on standard Wright-stained smears but require supravital staining with methylene blue or brilliant cresyl blue [4]. In our patient, both bite cells (Figure 2) and Heinz bodies (Figure 4) were identified, providing strong morphological evidence of oxidative hemolysis. The presence of microcytosis and hypochromia in this case is atypical for G6PD deficiency alone and may indicate concomitant iron deficiency or thalassemia trait, although further testing was not performed. Alternatively, chronic hemolysis with compensatory erythropoiesis can sometimes produce microcytic indices due to iron diversion.

Pancytopenia and bone marrow findings.

An intriguing aspect of this case is the presence of pancytopenia on two separate occasions (Table 1 and 2). G6PD deficiency classically causes hemolytic anemia without affecting white blood cells or platelets. Pancytopenia in this context suggests either an overlapping condition or a secondary effect of severe hemolysis. The bone marrow study revealed erythroid hyperplasia with megaloblastic changes, which is consistent with increased red cell turnover and possible folate deficiency due to chronic hemolysis [1]. Megaloblastic changes may also arise from concomitant vitamin B12 or folate deficiency; unfortunately, these levels were not measured. It is plausible that the patient's poor nutritional status or increased folate demand contributed to the pancytopenia. After folic acid supplementation and transfusion, his leukocyte and platelet counts normalized, supporting the hypothesis that folate depletion played a role. This case highlights the importance of evaluating for nutritional deficiencies in patients with chronic hemolysis and providing appropriate supplementation.

Hepatosplenomegaly and extramedullary hematopoiesis.

Ultrasound demonstrated hepatosplenomegaly, which is not a typical feature of G6PD deficiency unless there is chronic hemolysis with extramedullary hematopoiesis or secondary iron overload [2]. In our patient, the organomegaly likely reflects the compensatory expansion of the reticuloendothelial system due to chronic red cell destruction. The ascites was mild and resolved after improvement of anemia; its etiology remains unclear but could be related to cardiac overload or hepatic congestion.

Genetics and variants.

More than 200 G6PD mutations have been described, with G6PD A- (common in Africans) and G6PD Mediterranean (common in Middle Easterners and South Asians) being the most frequent variants associated with hemolysis [6]. The Mediterranean variant typically causes more severe hemolysis. Although our patient's ethnic background was not specified, the chronic relapsing course with marked anemia suggests a Class I or II variant (severe deficiency). Genetic testing was not performed but could provide prognostic information and family counseling.

Management and prevention.

The mainstay of management for G6PD deficiency is avoidance of oxidative stressors [7]. In this case, the patient had been using anti-inflammatory medications, which may have precipitated the hemolytic episode. Non-steroidal anti-inflammatory drugs (NSAIDs) are generally considered unsafe in G6PD deficiency, although the risk varies by specific agent [7]. He was advised to discontinue these drugs

and received a comprehensive list of medications to avoid (e.g., sulfonamides, nitrofurantoin, dapsone, methylene blue, and high-dose vitamin C). During severe hemolytic crises, supportive care with blood transfusions is life-saving [7]. Our patient responded well to transfusion and folic acid. It is also prudent to screen for G6PD deficiency in family members, as the condition is hereditary, though this was not documented in the present case.

Limitations. This report has several limitations. First, confirmatory genetic testing for the G6PD mutation was not performed. Second, vitamin B12 and folate levels were not measured, leaving the cause of megaloblastoid changes speculative. Third, the specific oxidative trigger for the current episode could not be definitively identified. Despite these gaps, the case clearly demonstrates the cardinal features of G6PD deficiency and the necessity of maintaining a broad differential for recurrent hemolysis.

CONCLUSION

G6PD deficiency is an underrecognized cause of chronic hemolytic anemia in adults. This case emphasizes that a meticulous review of the peripheral blood smear for bite cells and Heinz bodies, coupled with a low threshold for performing quantitative G6PD assay, can establish the diagnosis even in the absence of a classic family history or known trigger. The presence of pancytopenia and megaloblastic bone marrow changes should not dissuade clinicians from considering G6PD deficiency; rather, these findings may reflect superimposed nutritional deficiencies that are reversible with appropriate supplementation. Early diagnosis enables the implementation of preventive strategies—avoidance of oxidative drugs and fava beans—and reduces the risk of life-threatening hemolytic crises. As this case illustrates, G6PD deficiency should be included in the differential diagnosis for any adult with unexplained, recurrent hemolytic anemia.

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