CASE REPORT

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Coexistence of G6PD Deficiency and Hereditary Spherocytosis: Challenges in Diagnosis and Management

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Abstract

Glucose-6-phosphate dehydrogenase (G6PD) deficiency and hereditary spherocytosis (HS) are distinct haematological disorders with differing genetic causes. Their coexistence is rare and presents diagnostic and therapeutic challenges. We report the case of a 38-year-old Indian man with a known history of G6PD deficiency since childhood, who presented with progressive fatigue, jaundice, and dark-coloured urine over a one-week period. Laboratory investigations revealed spherocytes on peripheral blood smear, increased osmotic fragility, and elevated mean fluorescence intensity on the eosin-5'-maleimide (EMA) binding test, confirming the diagnosis of coexisting G6PD deficiency and hereditary spherocytosis. The patient was managed with inpatient supportive care including intravenous hydration, and close laboratory monitoring. The patient showed clinical improvement and was advised lifestyle modifications and follow-up. This case emphasizes the need for considering overlapping genetic disorders in haemolytic anaemia and highlights the utility of advanced diagnostics like the EMA binding test.

Key words: G6PD deficiency, hereditary spherocytosis, haemolytic anaemia, genetic disorders, jaundice.

Introduction

G6PD deficiency is the most common enzyme deficiency seen in humans[1]. It tends to be asymptomatic throughout life except in situations associated with oxidative stress when a haemolytic crisis may ensue. In some patients a mild-severe, chronic haemolysis has been described[1]. Hereditary spherocytosis arises from mutations in genes coding for red cell membrane proteins such as spectrin, ankyrin, and band 3, which result in spheroidal red cells with reduced deformability and premature destruction in the spleen[2]. Both disorders independently cause haemolytic anaemia, but their simultaneous occurrence is exceedingly rare and complicates diagnosis and treatment[3]. This report describes such a case with a focus on the diagnostic process and clinical management.

Case Description

A 38-year-old Indian man presented to the emergency department with progressive fatigue, yellowish discoloration of the skin and eyes (jaundice), and dark-coloured urine for one week. The patient reported experiencing similar but intermittent episodes of jaundice since childhood, often associated with infections or minor illnesses. He was diagnosed with G6PD deficiency during childhood after an episode of acute haemolysis triggered by an infection. The patient had no prior history of blood transfusion, chronic illnesses, or other haematological disorders. He denied any recent drug intake, fava bean consumption, or exposure to known oxidative agents. His family history was unremarkable, with no relatives diagnosed with hereditary blood disorders.

On physical examination, the patient appeared mildly icteric, with stable vital signs. Abdominal examination revealed mild splenomegaly without hepatomegaly or palpable lymphadenopathy. There were no signs of heart failure or other systemic involvement. Initial laboratory investigations revealed a haemoglobin level of 8.2 g/dL, an elevated reticulocyte count at 12.6%, and normal mean corpuscular volume (MCV) of 78.8 fL. The peripheral blood smear demonstrated prominent spherocytes and anisocytosis, along with occasional polychromasia. Biochemical tests showed elevated total bilirubin at 5.3 mg/dL (predominantly indirect), elevated lactate dehydrogenase (LDH) at 517 IU/L, and markedly decreased haptoglobin levels (<10 mg/dL), indicating ongoing haemolysis. Vitamin B12 and folic acid levels were within normal range. The direct Coombs test was negative, ruling out immune-mediated haemolysis. A dye decolourisation method test was done which showed that decolourisation had not occurred even after 3 hours (Range in normal subjects: 30 - 60 minutes) indicating the presence of G6PD deficiency. The osmotic fragility test revealed increased fragility of red blood cells. The Eosin-5'-maleimide (EMA) binding test was performed, demonstrating a mean fluorescence intensity (MFI) of 0.84, suggestive of hereditary

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spherocytosis (normal >0.85).

Upon admission, the patient was carefully monitored and treated with intravenous hydration to maintain renal perfusion and prevent haemoglobinuria-related complications. The patient received supportive care for mild splenomegaly. Genetic counselling was provided, where the patient was informed about the autosomal dominant inheritance pattern of hereditary spherocytosis and the X-linked inheritance of G6PD deficiency. He was advised regarding the risk of transmitting these conditions to offspring, the importance of avoiding oxidative triggers such as fava beans and sulfonamides, and the need for regular follow-up. The patient's clinical condition gradually improved over the course of hospitalisation. At discharge, his haemoglobin was 9.2 g/dL, total bilirubin dropped to 4.8 mg/dL, and LDH normalised to 440 IU/L.

He was instructed to follow-up at the haematology clinic for long-term monitoring, with emphasis on lifestyle modifications, early recognition of haemolytic crises, and periodic blood tests.

Table I: Laboratory investigations.

Parameter	At Admission	At Discharge	Reference Range
Haemoglobin (g/dL)	**8.2**	9.2	13.5 - 17.5
Reticulocyte Count (%)	**12.6**	–	0.5 - 2.5
Mean Corpuscular Volume (fL)	78.8	87	80 - 100
Total Bilirubin (mg/dL)	**5.3**	4.8	0.3 - 1.2
Indirect Bilirubin (mg/dL)	**4.5**	4.1	0.2 - 1.0
Lactate Dehydrogenase (IU/L)	**517**	440	140 - 280
Haptoglobin (mg/dL)	**<10**	–	30 - 200
EMA Binding Test MFI	**0.84**	–	>0.85 (Normal)

Differential Diagnosis

Given the clinical presentation of haemolytic anaemia, jaundice, dark urine, and splenomegaly, several differential diagnoses were considered before concluding the coexistence of G6PD deficiency and hereditary spherocytosis. Autoimmune haemolytic anaemia (AIHA) was an important consideration due to the presence of spherocytes, but the negative direct Coombs test ruled out immune-mediated haemolysis. No history of autoimmune disorders, drug exposure, or other triggers supported AIHA. Thalassaemia and hereditary elliptocytosis (HE) were also considered. Thalassaemia typically presents with microcytic anaemia and abnormal haemoglobin electrophoresis patterns, which were absent in this patient. He would have manifested primarily with elliptocytes on the peripheral smear, unlike the spherocytes observed here. Other enzymopathies such as pyruvate kinase deficiency were excluded based on enzyme assay results and the clinical picture. The definitive diagnosis was supported by history of G6PD deficiency, elevated osmotic fragility, and abnormal EMA binding test findings.

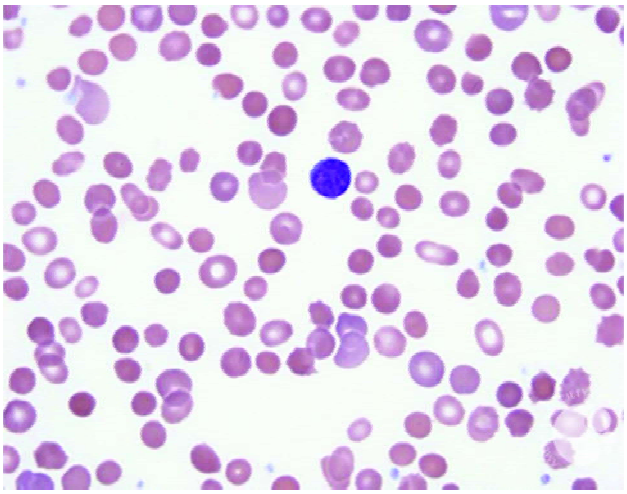

Fig. 1: *Spherocytes in Peripheral blood film.*

Discussion

This case highlights the coexistence of combined intra and extravascular haemolysis mechanisms, i.e., hereditary spherocytosis which is primarily extravascular (splenic destruction), and G6PD deficiency which is intravascular (oxidative stress-mediated).The diagnostic complexity was posed by the rare coexistence of G6PD deficiency and hereditary spherocytosis[3]. Both disorders independently lead to haemolytic anaemia, jaundice, and splenomegaly, but their combination may obscure a clear diagnosis without comprehensive evaluation. The EMA binding test has demonstrated higher sensitivity than traditional osmotic fragility testing and serves as a useful tool in such complex presentations[4]. Genetic testing for specific mutations in ANK1, SPTA1, SPTB, or G6PD could further confirm the diagnosis and guide family screening but was not performed due to logistic constraints[5].

Management of this patient focused on supportive care during the acute haemolytic crisis. Intravenous hydration was prioritised to prevent renal damage from haemoglobinuria[6]. Serial laboratory monitoring guided ongoing management. A multidisciplinary approach ensured tailored care, and genetic counselling provided clarity on inheritance patterns and the importance of preventive measures[3,6]. The role of splenectomy was discussed but deferred, as it is typically reserved for severe or refractory cases of hereditary spherocytosis[3,6]. The patient was discharged with clear advice to avoid haemolytic triggers, maintain regular follow-up, and monitor for early

signs of haemolytic episodes. Chronic haemolysis in dual pathology may lead to pigment gallstones, pulmonary hypertension, iron overload, or leg ulcers and renal dysfunction which was currently not present in the patient[7]. Periodic ferritin and abdominal ultrasound evaluations are recommended.

spherocytosis is a rare but significant diagnostic entity. A structured diagnostic approach including the EMA binding test and consideration of genetic analysis is crucial to avoid misdiagnosis. A multidisciplinary team-based management strategy ensures optimised care, and long-term follow-up focuses on patient education, lifestyle modifications, and

Table II: Drugs/conditions, which can lead to haemolysis in patients with G6PD deficiency[8].

Category	Examples	Remarks / Severity
Drugs – High-Risk	Primaquine, Chloroquine, Hydroxychloroquine, Quinine	Antimalarials. Primaquine is the most classic and severe
	Sulfonamides (Sulfamethoxazole, Sulfadiazine, Sulfasalazine), Dapsone	Very common cause; avoid in all G6PD patients
	Nitrofurantoin	Often prescribed for UTI; strong haemolytic trigger
	Rasburicase	Very high risk; contraindicated in G6PD deficiency
	Methylene blue	For methemoglobinemia '! dangerous in G6PD deficiency
Drugs – Moderate/Reported Risk	Chloramphenicol, Nalidixic acid, Ciprofloxacin (older FQs), Phenazopyridine	Less common but documented
	High-dose Aspirin, Vitamin K analogues	Rare, dose-dependent
Food	Fava beans (Broad beans)	Classic favism; can cause severe acute haemolysis
Infections	Bacterial: Pneumonia, Sepsis, Typhoid, UTI	Most common real-world trigger of haemolysis
	Viral: Hepatitis, Influenza, CMV	Viral oxidative stress worsens haemolysis
	Parasitic: Malaria	Dual effect: parasite + treatment (primaquine/quinine)

Review of Literature

G6PD deficiency is a common X-linked enzymopathy affecting over 400 million people globally, especially in Asian, Mediterranean, and African populations[1]. It impairs the pentose phosphate pathway, reducing NADPH production, and making red cells vulnerable to oxidative damage from infections, drugs, or fava beans[8]. Hereditary spherocytosis is the most common inherited haemolytic anaemia in Northern Europe but occurs worldwide, caused by mutations in red cell membrane proteins such as spectrin, ankyrin, and band 3[2]. This leads to reduced deformability of red blood cells and premature splenic destruction[2].

The coexistence of G6PD deficiency and hereditary spherocytosis is exceptionally rare, with only a few case reports in the literature[3]. Their overlapping clinical features can complicate the diagnosis. Advanced tests such as the EMA binding test have improved the diagnostic process, particularly in cases with ambiguous osmotic fragility results[4]. Management remains supportive during acute haemolytic crises, while genetic counselling is essential for patient education regarding inheritance patterns and family planning[3,6].

Conclusion

The coexistence of G6PD deficiency and hereditary preventive strategies, contributing to a favourable prognosis.

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