CASE REPORT

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Hereditary Spherocytosis with Conjugated Hyperbilirubinaemia, Chronic Liver Disease and Portal Hypertension

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Abstract

Hereditary spherocytosis (HS) is the most common inherited haemolytic anaemia and is classically associated with anaemia, splenomegaly, and unconjugated hyperbilirubinaemia. Chronic liver disease and portal hypertension are rare and atypical manifestations, particularly in young adults. We report a 36-year-old male with a long-standing history of jaundice and transfusion-dependent anemia who presented with pancytopenia and massive splenomegaly. Laboratory evaluation revealed severe hyperbilirubinaemia with a striking predominance of conjugated bilirubin, despite clear biochemical evidence of ongoing haemolysis. Peripheral blood smear demonstrated spherocytes, and the diagnosis of hereditary spherocytosis was confirmed by whole-genome sequencing identifying a pathogenic red blood cell membrane protein mutation. Liver stiffness assessment showed advanced hepatic fibrosis, and upper gastrointestinal endoscopy confirmed portal hypertension. Other causes of chronic liver disease, including autoimmune, metabolic, infectious, and inherited hepatobiliary disorders, were systematically excluded. The predominant conjugated hyperbilirubinaemia was attributed to secondary hepatocellular dysfunction and intrahepatic cholestasis resulting from long-standing haemolysis and transfusion burden. The patient was managed conservatively with blood transfusions, folic acid supplementation, and non-selective beta-blockers, while splenectomy was deferred due to portal hypertension. This case highlights a rare hepatic manifestation of hereditary spherocytosis and emphasizes that predominant conjugated hyperbilirubinaemia does not exclude hemolytic anaemia, particularly in patients with long-standing disease and secondary hepatic involvement.

Introduction

Hereditary spherocytosis (HS) is the most common inherited haemolytic anaemia, resulting from structural defects in red blood cell membrane proteins, most commonly ankyrin, spectrin, band 3, and protein 4.2[1,4]. These defects lead to loss of membrane surface area, reduced erythrocyte flexibility, and the formation of spherical red blood cells that are prone to sequestration and destruction within the spleen[1]. The condition exhibits considerable genetic and phenotypic heterogeneity, with autosomal dominant, autosomal recessive, and sporadic inheritance patterns[1,3]. Clinical manifestations range from asymptomatic disease to severe, transfusion-dependent haemolytic anaemia presenting early in life[1,2].

The classical clinical triad of HS includes anaemia, jaundice, and splenomegaly, with additional complications such as reticulocytosis, pigment gallstone disease, and episodic haemolytic crises[1,5]. Hepatobiliary involvement is commonly limited to unconjugated hyperbilirubinaemia and cholelithiasis; however, the development of chronic liver disease (CLD) and portal hypertension is distinctly uncommon and sparsely reported in the literature[6]. When present, these complications may arise due to chronic haemolysis, transfusion-related iron overload, long-standing hypersplenism, and progressive hepatic vascular and parenchymal injury, posing significant diagnostic and therapeutic challenges[7,8]. Reporting such rare associations is essential to improve recognition, facilitate timely diagnosis, and guide optimal long-term management[2].

Case Presentation

A 36-year-old male presented with fever and chills for one week, abdominal pain for 15 days, productive cough for four days, and progressive dyspnoea on exertion for the past three years. He had a history of jaundice and anaemia (Table I) since fifteen years of age and had received multiple blood transfusions over the period of time, frequency being once or twice in every 4 to 5 years, with the first transfusion administered during childhood following hernioplasty. There was no history of alcohol consumption, hepatotoxic drug use, or known family history of haemolytic anaemia or liver disease.

On examination, the patient was malnourished, icteric, febrile, tachycardic, and dyspneic, with marked pallor. Abdominal examination revealed massive splenomegaly, while cardiovascular and neurological examinations were

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normal. Laboratory evaluation (Table II) showed severe anemia (haemoglobin 5.4 g/dL), leukopenia (total leukocyte count 3.6 × 10^3/µL), thrombocytopenia (platelet count 85,000/µL), Corrected reticulocyte count was 3.21%, Immature platelet fraction was 13% (signifies optimal bone marrow function) and severe hyperbilirubinaemia (total bilirubin 75.9 mg/dL) with a predominant conjugated fraction (direct bilirubin 66.4 mg/dL). Evidence of ongoing haemolysis was present, including markedly reduced haptoglobin levels (<10 mg/dL). Peripheral blood smear examination revealed numerous spherocytes, suggestive of hereditary spherocytosis.

Table I: Past available medical records of the patient signifying long standing aneamia and indirect hyperbilirubinaemia.

Parameter	2013	2021	2023	2024
Pre-Transfusion Haemoglobin (g/dL)	5.0	6.7	8.5	7.6
Post-Transfusion Haemoglobin (g/dL)	6.0			
Total Bilirubin (mg/dL)	11.2	–	5.9	5.98
Direct Bilirubin (mg/dL)	4.2	–	1.0	1.59
Indirect Bilirubin (mg/dL)	7.0	–	4.9	4.39
AST (U/L)	28	–	59	21
ALT (U/L)	31	–	42	27
Total Protein (g/dL)	6.8	–	6.5	6.09
Albumin (g/dL)	4.3	–	3.4	4.17
ALP (U/L)	–	–	192	59

Table II: Investigations during the hospital stay signifying direct hypebilirubinaemia and severe anaemia.

Parameter	28/10/ 2025	31/10/ 2025	01/11/ 2025	04/11 2025
Pre-Transfusion Haemoglobin (g/dL)	9.7	9.6	5.1	8.1
Post-Transfusion Haemoglobin (g/dL)			7.4	
Total Bilirubin (mg/dL)	75.9	12.3	8.9	7.1
Direct Bilirubin (mg/dL)	66.4	8.4	6.1	4.4
Indirect Bilirubin (mg/dL)	9.5	3.9	2.8	2.7
AST (U/L)	30	20	25	36
ALT (U/L)	47	49	58	82
Total Protein (g/dL)	8.2	6.0	5.8	6.2
Albumin (g/dL)	4.4	3.4	3.2	3.6
ALP (U/L)	84	45.38	48	67

Liver stiffness assessment by transient elastography demonstrated advanced hepatic fibrosis (14.6 kPa, consistent with F3 fibrosis). Upper gastrointestinal endoscopy showed prominent gastric vein, confirming

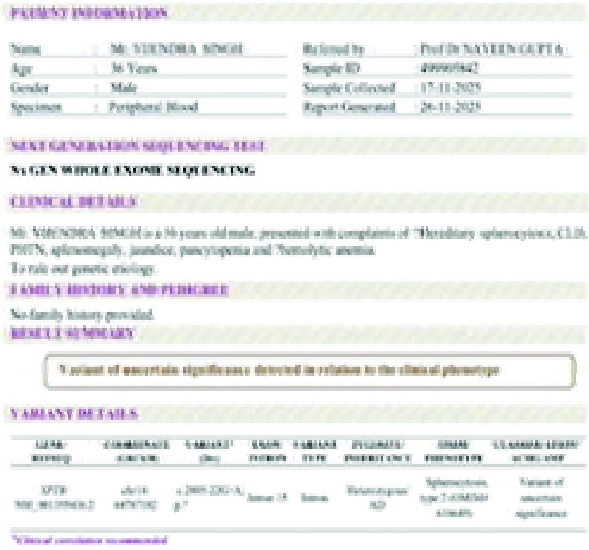


Fig. 1: *Shows variant of unknown significance in whole genome sequencing, confirming diagnosis of hereditary spherocytosis.*

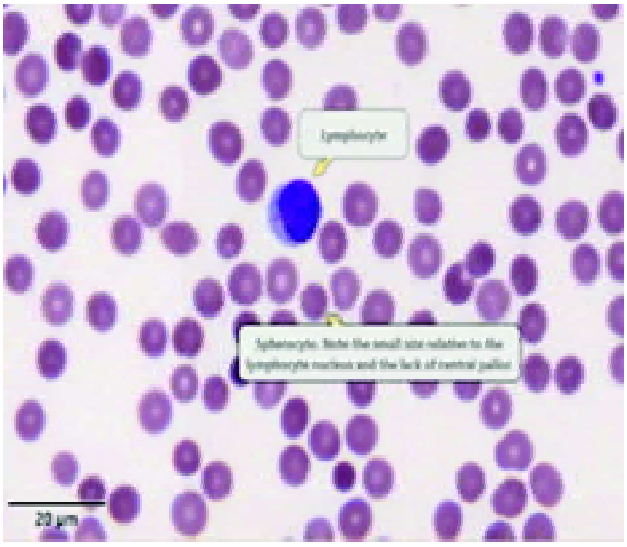


Fig. 2: *Peripheral blood smear of the patient showing characterstic spherocytes.*

portal hypertension. Whole-genome sequencing identified a pathogenic mutation that is Genetic variant of uncertain significance (VUS) involving a red blood cell membrane protein. Thus, in prescence of characterstic peripheral blood smear, and signs of haemolysis the diagnosis of hereditary spherocytosis was confirmed. Differential diagnosis, including autoimmune haemolytic anaemia (negative direct and indirect coombs test), thalassaemia (Normal Hb Electrophoresis), Wilson's disease (Serum Cerruloplasmin level - 16.2 which was normal), Hereditary hyperbilirubinaemia syndromes like Dubin Johnson, Rotor Syndrome (prescence of severe haemolysis is not seen in

these conditions) Benign Intrahepatic Cholestasis syndrome (Absence of recurrent self limiting episodes of Jaundice in the patient), and parvovirus B19 infection (no reticulocytopenia/aplastic crisis features) were systematically excluded based on clinical findings, laboratory evaluation, imaging, and genetic confirmation. Also, no familial association was found on pedigree analysis of the patient.

During hospitalisation, the patient was managed conservatively. He received 2 units packed red blood cell transfusions to correct severe anaemia and maintain haemoglobin levels above 7 g/dL. Empirical intravenous ceftriaxone was administered at a dose of 1 g twice daily for suspected infection. Oral prednisolone at a dose of 15 mg once daily was initiated during the initial diagnostic evaluation when immune-mediated haemolysis was considered and later tapered and discontinued. Supportive management included oral folic acid 5 mg once daily, multivitamin supplementation, and paracetamol 650 mg as required for fever. The patient remained haemodynamically stable throughout hospitalisation.

Following confirmation of hereditary spherocytosis, long-term folic acid supplementation was continued. In view of portal hypertension with esophageal varices, non-selective beta-blocker therapy with propranolol was initiated at a dose of 20 mg twice daily for primary prophylaxis. Splenectomy was considered but deferred due to the presence of portal hypertension and advanced hepatic fibrosis. The patient was discharged with advice for close follow-up under general medicine, haematology services. The patient has been regularly following up on outpatient basis in General Medicine OPD since last 5 months and is being adviced conservative management for CLD with Portal Hypertension and Folic acid supplementation for HS. His Condition has been stable and no blood transfusion has been required since his discharge from the hospital.

Discussion

HS is usually diagnosed in childhood; however, milder or atypical phenotypes may remain undiagnosed until adulthood, particularly in resource-limited settings[1,2]. In the present case, despite a long-standing history of jaundice and transfusion dependence since early childhood, diagnosis was delayed until adulthood, highlighting the diagnostic challenges associated with atypical presentations.

Diagnosis of HS relies on characteristic clinical features, laboratory evidence of haemolysis, and peripheral blood smear findings[2]. Specialised investigations such as eosin-5-maleimide binding assays and osmotic fragility testing may support the diagnosis[9], while genetic testing has emerged as a crucial tool in confirming the diagnosis, particularly in complex cases with overlapping haematologic and hepatic features[3,5]. In this patient, whole-genome sequencing was pivotal in establishing the diagnosis and excluding alternative aetiologies.

Haemolytic anaemias classically result in unconjugated hyperbilirubinaemia due to increased red cell breakdown[1,2]. However, this patient exhibited marked predominance of conjugated hyperbilirubinaemia, an unusual finding in isolated haemolysis. This pattern is best explained by secondary hepatocellular dysfunction and intrahepatic cholestasis resulting from long-standing haemolysis, chronic bilirubin overload, and progressive hepatic injury[11], iron overload due to repeated transfusions, congestive hepatopathy due to chronic anaemia, rarely due to coexisting inherited conjugation/excretion defects like Dubin – Johnson Syndrome and Rotor Syndrome, biliary obstruction[13]. Chronic haemolytic states have also been linked to porto-sinusoidal vascular disease and non-cirrhotic portal hypertension, which can impair bile canalicular transport and contribute to conjugated hyperbilirubinaemia[10,14]. Repeated transfusions and sustained haemolysis further promote hepatic oxidative stress, Kupffer cell activation, and progressive fibrosis, culminating in impaired excretion of conjugated bilirubin[7,12]. "In this patient, predominant conjugated hyperbilirubinaemia was most consistent with secondary hepatocellular dysfunction and intrahepatic cholestasis related to long-standing haemolysis and transfusion burden, as alternative inherited conjugation or excretory defects were excluded on genetic testing."

The coexistence of hereditary spherocytosis with chronic liver disease and portal hypertension is rare and sparsely reported[7]. What makes this case particularly unique is the presence of advanced hepatic fibrosis and clinically significant portal hypertension with esophageal varices at a young age, in the absence of other identifiable causes of chronic liver disease[10]. This expands the recognised hepatic spectrum of HS and highlights the potential for progressive liver injury in long-standing disease.

Management of HS in the presence of portal hypertension is challenging. While splenectomy remains the definitive treatment for moderate to severe HS, the presence of portal hypertension significantly increases perioperative bleeding risk[11]. Therefore, individualised management with supportive care, optimisation of liver disease, careful risk – benefit assessment, and multidisciplinary decision-making is essential in such complex clinical scenarios.

Conclusion

This case highlights a rare and clinically significant association between hereditary spherocytosis and chronic liver disease with portal hypertension. It also demonstrates

that predominant conjugated hyperbilirubinaemia may occur in long-standing haemolytic disorders due to secondary hepatocellular dysfunction and cholestasis. A high index of suspicion for inherited haemolytic anaemia should be maintained in patients presenting with chronic jaundice, splenomegaly, and unexplained liver disease. Early diagnosis, supported by genetic testing, is essential to prevent diagnostic delay and guide appropriate management, particularly regarding the timing and feasibility of splenectomy. This case highlights that predominant conjugated hyperbilirubinaemia does not exclude haemolytic anaemia and may reflect secondary hepatic involvement in long-standing disease.

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