Clin. Lab. 2026;72:XXX-XXX

CASE REPORT

Abnormal Liver Function with Low Glycated Hemoglobin: a Case of Hereditary Spherocytosis Concealed by Liver Disease Symptoms

Zhuan Zheng, Yaner Qian

Department of Medical Laboratory, Shaoxing People's Hospital, Shaoxing, P.R. China

SUMMARY

Background: **Hereditary spherocytosis (HS), a familial hemolytic disorder caused by red blood cell membrane defects, leads to increased red blood cell destruction. It manifests as jaundice, hemolytic anemia, and splenomegaly. HS patients, due to chronic hemolysis, are prone to developing bile duct or gallbladder stones, and some primarily present with 'cholelithiasis' as their main clinical manifestation.**
Methods: **We reported a case of a patient who was admitted for biliary colic due to choledocholithiasis and was ultimately diagnosed with HS. We conducted a retrospective analysis of this hospitalized patient's clinical manifestations, laboratory test results, and diagnostic process. The evaluated parameters encompassed complete blood count, peripheral blood smear analysis, biochemical markers (including liver function and HbA1c), and iron metabolism. To confirm the diagnosis, the patient's samples were sent to Dean Medical Laboratory Center for genetic testing. By employing high-throughput targeted sequencing technology, the laboratory staff screened multiple erythrocyte membrane protein-related genes.**
Results: **Laboratory test results showed that the patient had a decreased red blood cell count and hemoglobin levels, markedly reduced HbA1c values below the normal reference range, and elevated total bilirubin (TBIL) levels (684.0 µmol/L), predominantly direct bilirubin. Genetic testing confirmed the diagnosis of HS.**
Conclusions: **The clinical laboratory's identification and analysis of abnormal indicators (e.g., low HbA1c and elevated bilirubin) offer crucial diagnostic insights for clinicians. Integrating complete blood count, peripheral blood smear examination, and genetic testing enables accurate diagnosis of hematologic disorders, underscoring the essential role of laboratory medicine in multidisciplinary teamwork.**
(Clin. Lab. 2026;72:xx-xx. DOI: 10.7754/Clin.Lab.2025.250572)

Correspondence:
Yaner Qian
Department of Medical Laboratory
Shaoxing People's Hospital
Shaoxing 312000
P.R. China
Phone: +86 15958581397
Email: 67850996@qq.com

Case Report accepted May 30, 2025

KEYWORDS

hereditary spherocytosis, glycated hemoglobin, hyperbilirubinemia

INTRODUCTION

Hereditary spherocytosis (HS) is a chronic hemolytic anemia caused by red blood cell membrane protein defects. While common in North America and Europe, it typically presents as sporadic cases in China [1]. The condition arises from gene mutations affecting membrane proteins, leading to chronic hemolysis with recurrent acute episodes characterized by anemia, jaundice, and splenomegaly [2]. Diagnosis is challenging due to

atypical presentations, especially in patients without family history [3,4]. Our case illustrates this difficulty: the patient initially presented with abdominal pain and jaundice resembling acute gallstone disease, accompanied by hyperbilirubinemia and an unusually low HbA1c level. Through collaborative efforts between laboratory specialists and clinicians, we ultimately established the correct diagnosis. This study examines how laboratory markers can improve HS diagnosis, addressing a critical need in clinical practice.

CASE PRESENTATION

A 20-year-old male presented on October 3, 2024, with a 3-day history of dull right upper abdominal pain. Physical examination revealed moderate jaundice without hepatosplenomegaly. Laboratory tests showed:
Red blood cell count: 3.64↓ (reference range: 4.30 - 5.80) $x10^{12}$/L;
Hemoglobin: 123.0↓ (reference range: 130 - 175) g/L;
Hematocrit: 0.347↓ (reference range: 0.40 - 0.50);
Reticulocyte count: 11.88↑% (reference range: 0.5% - 1.5%);
Liver function tests:
Alanine aminotransferase (ALT): 216.6↑ (reference range: 9.0 - 50.0) U/L
Aspartate aminotransferase (AST): 157.5↑ (reference range: 15.0 - 40.0) U/L
Total bilirubin (TBIL): 684.0↑ (reference range: 3.4 - 20.5) μmol/L
HbA1c: 1.9%↓ (reference range: 4.0% - 6.3%)
Iron metabolism indices, including serum iron and total iron-binding capacity, were within normal ranges. Viral and autoimmune liver disease screenings yielded negative results. Abdominal ultrasound detected common bile duct stones, gallbladder sludge deposition, and splenomegaly.
The patient had no history of diabetes, hepatobiliary disease, or long-term medication use. Peripheral blood smear examination revealed 30% spherocytes (Figure 1). To confirm the diagnosis, the patient's specimen was sent to Dean Medical Laboratory Center for genetic testing. By employing high-throughput targeted sequencing technology, the laboratory staff screened multiple erythrocyte membrane protein-related genes and identified a mutation in the SPTB gene (c.5494G>T) (Figure 2), which led to the definitive diagnosis of HS.

DISCUSSION

HS is characterized by defects in red blood cell membrane proteins, such as ANK1 and SPTB gene mutations, which lead to abnormal red blood cell morphology (spherocytosis). These defective cells are particularly vulnerable to destruction in the spleen, resulting in extravascular hemolysis. The hemolysis process causes hemoglobin to break down into large quantities of unconjugated bilirubin, thereby exceeding the liver's metabolic capacity. This excess bilirubin then binds with calcium, forming pigment gallstones [5]. In this case, the patient presented with clinical manifestations suggestive of cholelithiasis. The abnormal laboratory findings demonstrated the following key features: 1. Significantly low HbA1c levels coexisting with hyperbilirubinemia: HbA1c reflects the average blood glucose level during the red blood cell lifespan. Its reduction may be associated with the shortened red blood cell lifespan caused by HS [6,7]. The elevated indirect bilirubin results from increased red blood cell destruction. The combination of these two findings suggests hemolysis and provides important diagnostic clues. 2. Complete blood count (CBC) revealed decreased red blood cell counts and hemoglobin levels, consistent with mild anemia. Peripheral blood smear examination demonstrated characteristic spherocytes, providing strong preliminary evidence for HS diagnosis. 3. Genetic testing plays a crucial role in definitive diagnosis and laboratory verification. The SPTB gene mutation is a well-documented cause of HS, and genetic testing can provide definitive molecular diagnosis.
This case highlights the following key points for clinical laboratories to consider: 1. Comprehensive analysis of abnormal test results: Clinicians should recognize that the combination of low HbA1c and hyperbilirubinemia warrants suspicion of hemolytic disorders, rather than attributing these findings solely to glucose metabolism abnormalities or hepatobiliary diseases. 2. In-depth communication with clinicians: When laboratory results contradict clinical presentations, timely discussions about medical and family history can significantly narrow the differential diagnosis. 3. Expansion of laboratory testing: For patients suspected of having hemolytic disorders, essential diagnostic procedures-including peripheral blood smear examination, cellular morphology analysis, and targeted genetic testing - are indispensable. These tests complement automated detection systems by providing critical diagnostic information that may otherwise be missed.

CONCLUSION

In the early diagnosis of hematologic disorders, clinical laboratories play a pivotal role in sensitively detecting and comprehensively analyzing abnormal test indicators. This case illustrates how the combination of low HbA1c levels with elevated bilirubin levels, complemented by peripheral blood smear examination and genetic testing, provides crucial diagnostic guidance for clinical practice. Moving forward, enhancing collaboration between clinical laboratories and medical departments, streamlining testing workflows, and improving the interpretation of complex test results will be key strategies for advancing precision medicine.

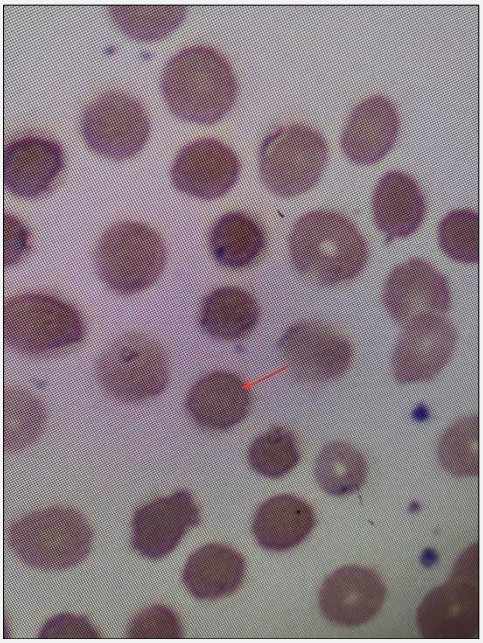

Figure 1. Microscopic examination of the patient's peripheral blood smear reveals spherocytes, as indicated by the arrows.

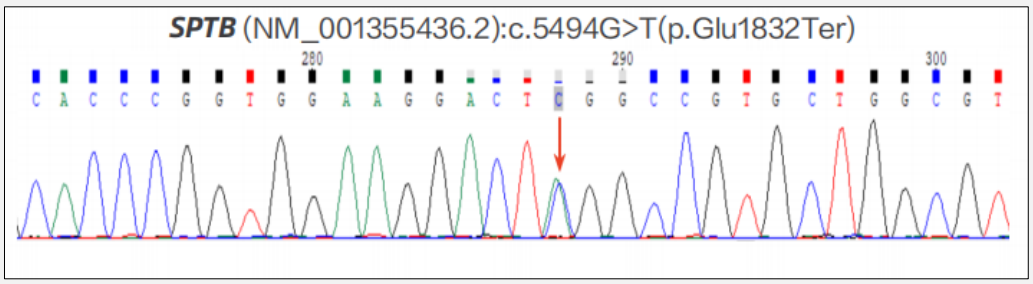

Figure 2. The Sanger sequencing chromatogram of the patient reveals a mutation site marked by the arrow.

Sources of Support:
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Interest:
All authors declare that they have no competing interests.

References:

1. Wang Y, Liu T, Jia C, et al. A novel variant in the SPTB gene underlying hereditary spherocytosis and a literature review of previous variants. BMC Med Genomics 2024 Aug;17(1):206. (PMID: 39135028)

2. Al Toub FA, Asseri AHO, Baig MR, Almalki NAR, Anwar F. Crosstalk: Biochemical Signatures and Clinical Implications in Rare Hereditary Hemolytic Anemias (Hereditary Spherocytosis). Curr Pharm Des 2025 Jan; Epub ahead of print. (PMID: 39865824)

3. Cheng J, Zhang L, Yao J, Zhao S, Jiang J. Clinical characteristics of hereditary spherocytosis with red blood cell membrane protein gene variants. Front Pediatr 2025 Feb;13:1523288. (PMID: 39995895)

4. Khillare KM, Vaishnav B, Doshi NI, Pailla R, Wadivkar A. Heresditary Spherocytosis: Unravelling the Diagnostic Challenges. Cureus 2024 Sep ;16(9):e70308. (PMID: 39463544)

5. Naamansen AB, Hansen DL, Petersen J, Glenthoj A, Sorensen HT, Frederiksen H. 10-Year Risk of Gallstones in Congenital Red Blood Cell Disorder Patients: A Nationwide Cohort Study. Am J Hematol 2025 Feb;100(2):229-35. (PMID: 39651840)

6. Wakuta N, Matsubayashi T, Oba K, et al. Usefulness of HbA1c Measurements by HPLC- and Immuno-Assay for Screening Unstable Hemoglobinopathy. Ann Clin Lab Sci 2023 Jan;53(1):134-9. (PMID: 36889775)

7. De Sanctis V, Soliman AT, Daar S, Di Maio S, Elsedfy H, Kattamis C. For Debate: Assessment of HbA1c in Transfusion Dependent Thalassemia Patients. Pediatr Endocrinol Rev 2020 Jun; 17(3):226-34. (PMID: 32741153)