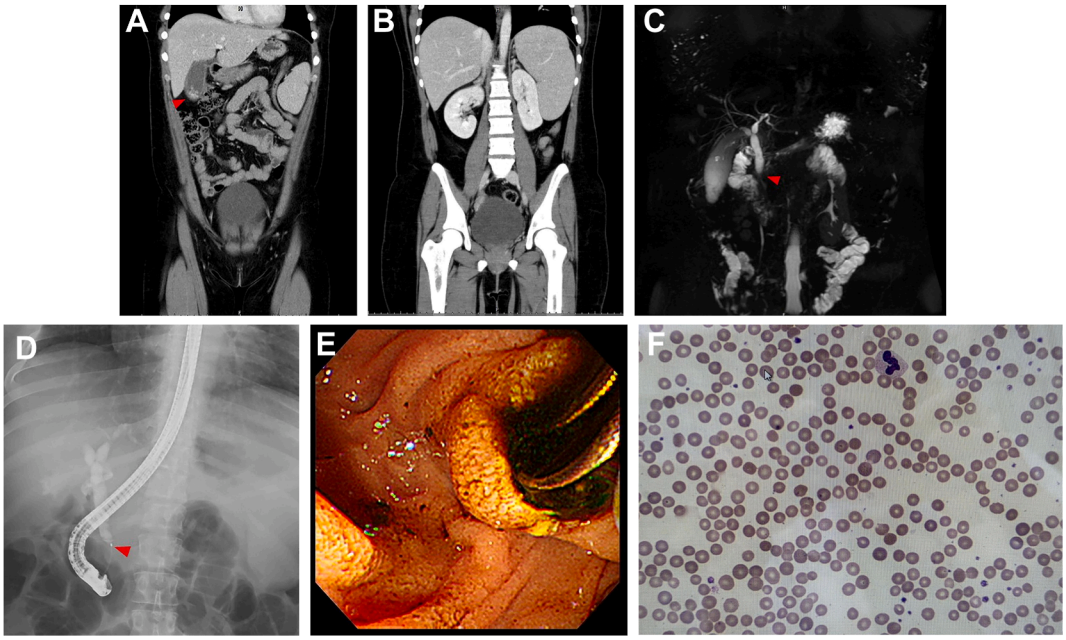
An Occult Etiology Behind the Episode of Obstructive Jaundice in a Young Woman

Meng-Hsing Ho,[1] Chih-Wei Yang,[2] and Yu-Guang Chen[3,4,5]

[1]Division of General Surgery, Department of Surgery, Tri-Service General Hospital, National Defense Medical University, Taipei, Taiwan; [2]Division of Gastroenterology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical University, Taipei, Taiwan; [3]Division of Hematology/Oncology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical University, Taipei, Taiwan; [4]The Center for Cell Therapy and Regenerative Medicine, Tri-Service General Hospital, Taipei, Taiwan; and [5]Graduate Institute of Medical Sciences, National Defense Medical University, Taipei, Taiwan



Question: A 24-year-old woman presented to the emergency department with a 3-day history of spiking fevers, right upper quadrant abdominal pain, and progressive jaundice. Reviewing her history, she reported having a common cold about 1 week before presentation. She had neonatal jaundice requiring phototherapy and later noted intermittent skin yellowing during adolescence and early adulthood. She had no past medical history, medications, or relevant family history, except that her mother had mild asymptomatic hyperbilirubinemia (total bilirubin ~2.5 mg/dL) without follow-up. On examination, she exhibited noticeable yellow discoloration of the skin and sclera, consistent with jaundice. Palpation revealed mild right upper quadrant tenderness without rebound or guarding. Notably, on abdominal palpation, the spleen was palpable below the left costal margin. Initial laboratory evaluations revealed markedly elevated total and direct bilirubin levels at 30.2 mg/dL and 15.6 mg/dL, respectively. Liver transaminases were elevated, with aspartate aminotransferase and alanine aminotransferase levels of 125 U/L and 189 U/L, respectively, and the lactate dehydrogenase (LDH) level was 510 U/L. Severe normocytic anemia was identified (hemoglobin, 6.4 g/dL), while white blood cell and platelet counts remained within normal limits. Serum studies for infectious and autoimmune markers—including hepatitis B and C, human immunodeficiency virus, antinuclear antibodies, double-stranded DNA, and complement levels—were all within normal limits. Abdominal computed tomography demonstrated multiple gallstones (Figure *A*, *arrowhead*), gallbladder wall edema with mild thickening, and splenomegaly (Figure *B*). Magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography (ERCP) revealed a distal common bile duct stricture (Figures *C* and *D*, *arrowhead*) with biliary obstruction caused by multiple hard, dark brown to black pigment stones (Figure *E*). Stone extraction and biliary decompression were performed successfully, leading to resolution of her abdominal pain and cholestasis. Despite initial treatment, the patient continued to have unconjugated hyperbilirubinemia

(total bilirubin, 5.4 mg/dL; direct bilirubin, 2.3 mg/dL) for 2 months after the initial presentation, and splenomegaly of unclear etiology remained present.

In light of the persistent normocytic anemia documented in serial blood tests (with the peripheral blood smear shown in Figure *F*), what is the most probable etiology and underlying pathophysiologic mechanism responsible for her persistent jaundice and splenomegaly?

See the *Gastroenterology* website (www.gastrojournal.org) for more information on submitting to *Gastro* Curbside Consult.

Correspondence
Address correspondence to: Yu-Guang Chen, MD, PhD, Division of Hematology/Oncology, Department of Internal Medicine, Tri-Service General Hospital, No. 325, Sec. 2, Chenggong Road, Neihu District, Taipei City 114202, Taiwan. e-mail: song123456@mail.ndmctsgh.edu.tw; or song123456tw@gmail.com.

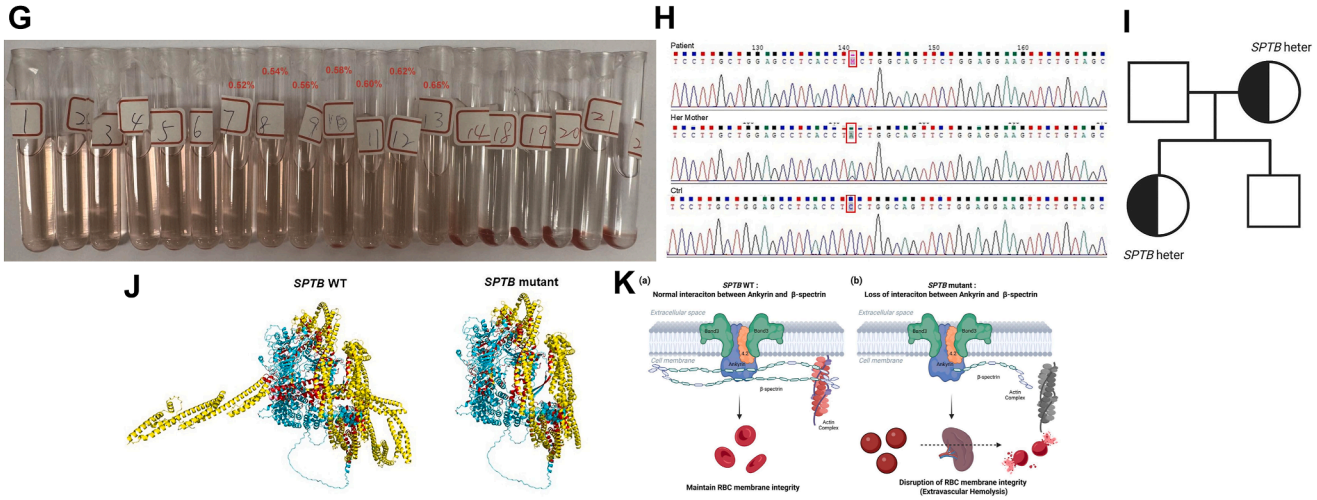
Acknowledgments
We thank Dr Yen-Lin Chen for performing the genetic examination, providing consultation, and analyzing the next-generation sequencing data. We also greatly appreciate the assistance of Dr Tong-Yu Hu for his expertise in predicting the molecular mechanism of the protein–protein interaction between *ANK1* and the mutant *SPTB* using AlphaFold 3 and PyMOL. Figure *K* was produced using BioRender.com. Ethical approval for issues related to human rights was granted by the Institutional Review Board of Tri-Service General Hospital (Registration No. TSGH-IRB A202515080).

Conflicts of interest
The authors disclose no conflicts.

Funding
This research was further supported by several grants from the National Science and Technology Council Funding & Awards (114-2314-B-016-004-MY2), VGH, TSGH, AS Joint Research Program (113DCA0200005), the Tri-Service General Hospital (TSGH-E-113225/TSGH-E-114227), and the National Defense Medical University (MND-MAB-D-114084) awarded to Y.G.C.

0016-5085/$36.00
http://doi.org/10.1053/j.gastro.2025.08.027

Answer to: Image 2: Hereditary Spherocytosis With Persistent Hemolytic Anemia



Establishing the Diagnosis

Based on the stones' appearance—hard and dark—there is a strong suggestion of a chronic hemolytic process, cirrhosis, or long-term parenteral nutrition, whereas brown pigment stones more often reflect an infectious etiology.[1] Although her clinical condition improved after the ERCP, indirect hyperbilirubinemia and elevated serum LDH levels persisted. Altogether, these findings indicated that his underlying hemolytic anemia was a key driver in the formation of both gallstones and intrahepatic pigment stones, ultimately leading to obstructive jaundice and cholecystitis. The diagnostic approach to hemolytic anemia begins with distinguishing intrinsic from extrinsic causes. Common extrinsic etiologies include autoimmune hemolytic anemia and microangiopathic hemolytic anemia. In this case, an autoimmune etiology was unlikely because both direct and indirect Coombs tests were negative. Additionally, the peripheral blood smear showed no fragmented red cells, and the platelet count remained within normal limits, making microangiopathic hemolytic anemia less probable.[2] Notably, the smear demonstrated spherocytes (Figure *F*), and osmotic fragility testing revealed hemolysis commencing at 0.65% NaCl and becoming complete at 0.52% NaCl (Figure *G*). These findings are characteristic of hereditary spherocytosis (HS), supporting it as the underlying cause. To further elucidate the genetic background of the patient and her family, whole-exome sequencing was performed on both the patient and her mother (shown in Supplementary Tables 1 and 2, respectively). This identified a novel heterozygous early termination mutation in the *SPTB* gene (Ref: ENST00000644917.1, *c.*3853 G>T(termination), p. E1285*), predicted to result in premature truncation of β-spectrin, a key cytoskeletal protein in erythrocyte membranes. Sanger sequencing confirmed the variant in both mother and daughter, consistent with autosomal-dominant inheritance (Figures *H* and *I*). AlphaFold 3–based protein interaction modeling, as presented in Figure *J* (structure visualization generated by PyMOL), depicts β-spectrin in yellow and ankyrin-1 in blue, with the red region indicating their interaction surface. The results suggest that this truncating mutation disrupts the interface between β-spectrin (encoded by *SPTB*) and ankyrin-1 (encoded by *ANK1*), thereby compromising red blood cell membrane stability and promoting chronic hemolysis.

Review

This case highlights the presence of an underlying inherited hematologic disorder as the cause of an acute episode of obstructive jaundice. In addition to the peripheral blood smear findings, a key feature that raises suspicion for HS in this case is the presence of the characteristics of gallstone and splenomegaly. This finding likely reflects a chronic hemolytic process and is notably distinct from what would be expected in patients with obstructive jaundice alone. HS is the most common inherited hemolytic anemia in Northern Europeans, with a prevalence of approximately 1 in 2000, whereas it is considerably rarer in Asian populations, with a prevalence of about 1 in 100,000.[3] Its primary pathogenic mechanism involves defects in red blood cell membrane proteins—commonly ankyrin, band 3, protein 4.2, α-spectrin, or β-spectrin—leading to decreased deformability and increased splenic sequestration.[4] Genetically, most cases of HS involve mutations in *ANK1*, followed by *SPTB* and other less common genes.[5]

In the Asian population, *SPTB* mutation is a relatively common genetic background. *SPTB* encodes β-spectrin, the rate-limiting subunit of the $\alpha_2\beta_2$-spectrin network that supports the erythrocyte membrane.[6] Mechanistically, approximately 70% of identified SPTB mutations introduce premature termination codons, implicating mechanisms such as nonsense-mediated messenger RNA decay,[7] nonsense-associated altered splicing, or production of truncated proteins in the

pathogenesis of HS,[8] ultimately leading to haploinsufficiency and weakened ankyrin–β-spectrin binding. The current case is further notable for the identification of a novel *SPTB* mutation (p. E1285*) with predicted structural impact of weakening β-spectrin–ankyrin binding, contributing to the phenotypic expression of HS within the family. Figure *K* illustrates the red blood cell membrane defect from this mutation, leading to chronic hemolysis. Although our computational simulation suggests a potential mechanism underlying this loss-of-function mutation, dedicated experimental studies are still required to validate its specific functional consequences.

Chronic hemolysis in HS increases the biliary excretion of unconjugated bilirubin, predisposing patients—often from a young age—to pigment gallstone formation.[9] Although many cases are asymptomatic, individuals with a high hemolytic burden may develop complications such as cholecystitis, obstructive jaundice, or intrahepatic stone formation. In HS patients presenting with biliary complications, ERCP plays a key role in the management of acute biliary obstruction.[5] The subsequent treatment when patients recover from acute episodes often involves cholecystectomy and, in selected cases, splenectomy. Splenectomy is typically considered for patients with severe anemia (hemoglobin, $<$8 g/dL; reticulocyte count, $>$10%), transfusion-dependence, persistent unconjugated hyperbilirubinemia, or other complications arising from hemolysis.[10] With the increasing availability of genomic testing, genetic evaluation is now more commonly recommended for younger patients presenting with indirect hyperbilirubinemia, pigment gallstones, or unexplained hepatobiliary disorders. This approach not only aids in establishing an accurate diagnosis but also supports appropriate family screening and genetic counseling.

Patient Outcome

Following evaluation of hemoglobin, bilirubin, and LDH levels after ERCP, the patient exhibited mild anemia (hemoglobin, 9.8 g/dL) without the need for transfusions, along with a modest elevation in unconjugated bilirubin (total bilirubin, 2.5 mg/dL). Given clinical indications and the potential risk of postoperative infectious complications, splenectomy was not advised. Instead, cholecystectomy alone was performed to prevent recurrent episodes of cholecystitis. To date, the patient has been under regular outpatient follow-up and has taken folic acid supplementation without significant or recurrent complications. In HS patients, folic acid is recommended to support the increased erythropoietic demand, although iron should be avoided unless deficiency is confirmed, due to the risk of overload, particularly in transfused patients.

Keywords: Hereditary Spherocytosis; *SPTB* Mutation; Obstructive Jaundice; Pigment Gallstones; Chronic Hemolytic Anemia.

References

1. Lammert F, Gurusamy K, Ko CW, et al. Gallstones. Nat Rev Dis Primers 2016;2:16024.
2. Go RS, Winters JL, Kay NE. How I treat autoimmune hemolytic anemia. Blood 2017;129:29712979.
3. Bolton-Maggs PH, Langer JC, Iolascon A, et al. Guidelines for the diagnosis and management of hereditary spherocytosis–2011 update. Br J Haematol 2012;156:3749.
4. Songdej D, Surapolchai P, Komwilaisak P, et al. Molecular characteristics of hereditary red blood cell membrane disorders in Thailand: a multi-center registry. Ann Hematol 2024;103:385393.
5. Delaunay J. Molecular basis of red cell membrane disorders. Acta Haematol 2002;108:210218.
6. Li S, Guo P, Mi L, et al. A novel SPTB mutation causes hereditary spherocytosis via loss-of-function of beta-spectrin. Ann Hematol 2022;101:731738.
7. Lindeboom RGH, Vermeulen M, Lehner B, et al. The impact of nonsense-mediated mRNA decay on genetic disease, gene editing and cancer immunotherapy. Nat Genet 2019;51:16451651.
8. Perrotta S, Della Ragione F, Rossi F, et al. Beta-spectrinBari: a truncated beta-chain responsible for dominant hereditary spherocytosis. Haematologica 2009;94:17531757.
9. Naamansen AB, Hansen DL, Petersen J, et al. 10-year risk of gallstones in congenital red blood cell disorder patients: a nationwide cohort study. Am J Hematol 2025;100:229235.
10. Iolascon A, Andolfo I, Barcellini W, et al. Recommendations regarding splenectomy in hereditary hemolytic anemias. Haematologica 2017;102:13041313.