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Complications of delayed diagnosis and challenges: successfully managed *SPTB* gene variant hereditary spherocytosis with hepatocellular jaundice—a case report

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Abstract

Background Hereditary spherocytosis is a rare genetic disorder of the red blood cell membrane that is characterized by anemia, jaundice, and splenomegaly; however, in the absence of family history and with unusual clinical presentation, the diagnosis might not be made until later in life.

Case presentation Here, we present a challenging case of genetically proven hereditary spherocytosis that involves the *SPTB* gene in a 23-year-old female patient from Ethiopia who had repeated medical visits for episodic jaundice and hepatosplenomegaly, with unusual features of conjugated hyperbilirubinemia, pancytopenia, normal reticulocyte count, and lack of family history, where the delay in diagnosis led to several complications. The patient was successfully managed with simultaneous splenectomy and cholecystectomy.

Conclusion This case underscores the importance of a thorough clinical examination, spending the time to review a case periodically without assuming the initial diagnosis is correct, and maintaining a healthy skepticism of inconsistent data to prevent misdiagnosis and mistreatment. The diagnostic delay highlights the need for increased awareness and familiarity with diagnostic modalities of hereditary spherocytosis among healthcare providers in Ethiopia.

Keywords Jaundice, Hereditary spherocytosis, Cholelithiasis, Hepatosplenomegaly, Case report

Introduction

Hereditary Spherocytosis (HS) is the most frequent genetic cause of hereditary hemolytic anemia that is associated with a defect in the red cell membrane and leads to a reduced life span of red blood cells [1]. Autosomal dominant inheritance occurs in about 75% of cases and 25% are owing to autosomal recessive inheritance or *de novo* mutations. The five important genes implicated in the pathophysiology of HS include ankyrin-1, alpha-spectrin, beta-spectrin, band-3, and protein 4.2, and have been linked to various clinical manifestations [2].

The diagnosis of HS is usually straightforward when there is a family history and typical clinical symptoms

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(anemia, jaundice, and splenomegaly with reticulocytosis) [3]. However, owing to atypical presentations that resemble liver disease [4–7] and the fact that family history is not always evident in mild and compensated illnesses, it might be difficult at times. The possible complications of HS include hepatosplenomegaly, gallstones, hematologic crises (hemolytic, megaloblastic, and aplastic crises), rarely secondary iron overload, and heart failure [2].

Several diagnostic tests are available for Hereditary Spherocytosis, with the combination of the eosin-5-maleimide (EMA) test and the acidified glycerol lysis test (AGLT) recommended. Other effective combinations include EMA with the osmotic fragility test (OFT) and OFT with AGLT. Although expensive, genetic testing may be necessary in certain clinical situations[1, 3, 8].

Epidemiologic data on hereditary spherocytosis in Black individuals is limited, with only a few case reports. This report presents a genetically confirmed case of HS from Ethiopia with an atypical clinical profile and sequelae that could have been prevented with early diagnosis. It intends to increase awareness of the occurrence of HS in our community and widen the diagnostic horizons of physicians in patients with unexplained jaundice. It also highlights surgical management and challenges.

Case presentation

Clinical history

A 23-year-old Ethiopian female patient presented with complaints of recurrent yellow discoloration of the eyes and skin lasting for 1 week, accompanied by fever, easy fatigability, abdominal pain with nausea, and vomiting. She also noted a long-standing, gradually enlarging bulge in the left side of her abdomen. She had no history of previous malaria attacks and was not from the visceral leishmaniasis endemic area.

She was born at home without any complications during the neonatal period. However, at the age of 6 years, she was taken to a hospital owing to yellow discoloration of the eyes (no records available). Subsequently, she had recurrent symptoms that resolved on their own. She had no history of blood transfusion. She is the eighth child in her family, with three sisters and four brothers, all of whom are alive along with her mother and father. None of her family members reported any symptoms.

During adulthood, she was admitted to a teaching tertiary referral hospital with the same medical problems 3 years back. After a battery of tests, including a bone marrow aspiration, the diagnosis of hyperreactive malarial splenomegaly syndrome and megaloblastic anemia was considered. She was discharged after 5 days of inpatient stay with folic acid, cyanocobalamin, and chloroquine. The abdominal ultrasound showed mild hepatomegaly and massive splenomegaly but no gallbladder stone. The bone marrow was normocellular marrow with trilineage hematopoiesis and erythroid hyperplasia, with no blast increment seen. The peripheral blood smear revealed mild poikiloanisocytosis with hypersegmented neutrophils and macrocytic red blood cells. The conclusion was normocellular bone marrow with erythroid hyperplasia, and the peripheral morphology was suggestive of megaloblastic changes.

She continued to have follow-ups every 3 months and the attending medical resident misdiagnosed her with iron deficiency anemia without strong evidence on her second visit and erroneously continued to take iron supplements until her current emergency presentation. She had around 11 follow-up visits, during which her hemoglobin levels varied between 7.3 and 9.6 g/dl and the laboratory technician repeatedly noted the presence of spherocytes on peripheral blood smear. However, reticulocyte counts were not done.

A year ago, she underwent evaluation by a hematologist at a private hospital. Although complete clinical information was inaccessible, iron and folic acid supplements were prescribed. The following data were available from the patient: hemoglobin level was 8.3 (normal range 11.5–16) g/dl, mean corpuscular volume (MCV) was 95.7 (normal range 80–100) fl, mean corpuscular hemoglobin (MCH) was 32 (normal range 32–36) pg, mean corpuscular hemoglobin concentration (MCHC) was 34.1 (normal range 32–36) g/dl, red cell distribution width (RDW) was 25.8 (normal range 11–16), total leukocytes count was 5.8×10^3/μl (normal range 4–10), platelet count was 324×10^3/μl (normal range 150–500), total bilirubin level was 4.2 (normal range 0.2–1.3) mg/dl, and direct bilirubin level was 2.1 (normal range 0–1.1) mg/dl.

Physical examination

Upon initial admission to the ward, she appeared pale but otherwise healthy. Her pulse rate was 118 beats per minute, temperature was 39.8 °C, and blood pressure was 90/60 mmHg. She had pale conjunctiva, icteric sclera, and no palpable lymph nodes. Her abdomen was soft, with a palpable spleen 22 cm below the left costal margin and a liver 8 cm below the right costal margin. Otherwise, examinations of the chest, cardiovascular, integumentary, musculoskeletal, and neurological systems were unremarkable.

Investigation

At the emergency visit, the white blood cell (WBC) count was 2.3×10^3/μl (reference range 3.8–11.8), hemoglobin was 6.1 (reference range 10.9–14.3) g/dl, MCV was 86.1 (reference range 75.5–95.3) fl, MCH was 31.7 (reference range 24.7–32.8) pg, MCHC was 36.8 (reference range

32.3–35.6) g/dl, RDW was 18.2 (reference range 12.3–17.7), and platelet count was 94×10^3/μl (reference range 179–408).

Liver function tests revealed elevated total bilirubin levels of 7.505 (reference range 0.1–1.2) mg/dl and direct bilirubin levels of 4.773 (reference range 0–0.2) mg/dl. Aspartate aminotransferase (AST) levels were 71 (reference range < 31) U/L, alanine aminotransferase (ALT) levels were 91 (reference range < 34) U/L, and alkaline phosphatase (ALP) levels were 90.03 (reference range 30–120) U/L. Serum lactate dehydrogenase (LDH) was elevated at 734 (reference range 120–300) IU/L, and both the direct and indirect Coombs tests were negative.

Iron studies showed low total iron binding capacity (TIBC) levels of 205 (reference range 265–497) μg/dl and markedly elevated serum ferritin levels exceeding 1000 ng/ml. Uric acid levels, lipid profiles, serum electrolytes, and renal function tests were all within normal limits. Serologic tests for syphilis, human immunodeficiency virus, hepatitis B and C, and antinuclear antibodies were non-reactive. Blood film for malaria and RK-39 test for visceral leishmaniasis were negative.

Peripheral smear found anisocytosis, macroovalocyte, scanty platelets, reduced WBC with differential neutrophil count of 54% with few hyper-segmented cells, lymphocyte count of 44%, monocyte count of 2%, no blast was seen, with the above pictures regarded as suspicious for megaloblastic anemia. No comment on spherocytes was given. The uncorrected reticulocyte count was normal [2.39% (reference range 0.3–3.0%); nevertheless, it was done 2 weeks after blood transfusion]. Both serum hemoglobin and protein electrophoresis results were also normal.

Abdominal computerized tomography (CT) scans revealed hepatomegaly, massive splenomegaly, ascites, and multiple gallbladder stones (Fig. 1). Severe pulmonary hypertension was detected on echocardiography.

A peripheral smear was purposefully evaluated to check for spherocytes, as they had been noted in previous follow-ups. The smear examined (2 weeks post-blood transfusion) revealed the presence of spherocytes along with anisocytosis and nucleated red blood cells (Fig. 2).

Diagnosis and treatment

With an initial impression of hepatosplenomegaly secondary to hematologic malignancy, coupled with sepsis of unknown origin and shock at the emergency department, the patient was resuscitated with three bags of normal saline. Treatment with meropenem and vancomycin

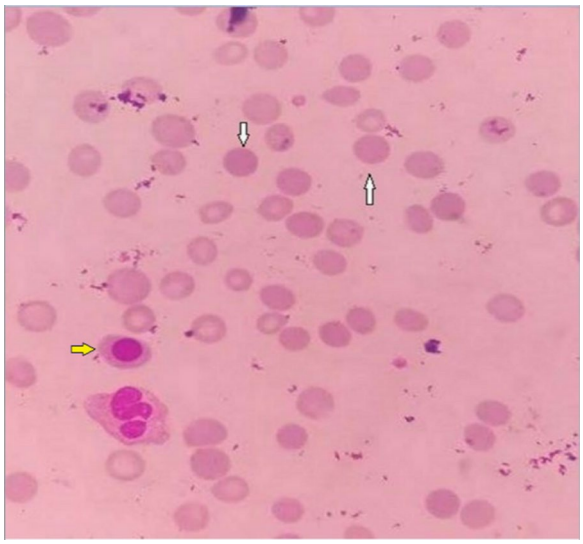


Fig. 2 Spherocytes are indicated by white arrows on the peripheral smear of the patient and nucleated red blood cells are indicated by yellow arrow



Fig. 1 Pre- and post-contrast-enhanced abdominal and pelvic computed tomography scan. Coronal reformatted post-contrast images in (**A** and **B**) demonstrated a markedly enlarged spleen and liver, measuring 30.2 cm and 20.5 cm on the craniocaudal dimension, respectively. Small amounts of free fluid were also seen in the pelvis. **C** An axial precontrast abdominal computed tomography scan image showing multiple hyperdense foci in the gall bladder neck, cholelithiasis (yellow arrow)

was initiated, and she required a noradrenaline drip and hydrocortisone 50 mg every 6 h for 48 h. Although blood cultures were sent after starting antibiotics, they came back negative. She was also transfused with four units of packed red blood cells.

Following ward admission, an in-depth analysis of the patient's history with laboratory findings of spherocyte on peripheral smear, elevated MCHC and RDW, negative direct and indirect coombs test, and normal hemoglobin electrophoresis, led to an impression of Hereditary Spherocytosis to rule out congenital dyserythropoietic anemia type 2, megaloblastic crisis precipitated by sepsis of unknown focus plus secondary iron overload was suspected. The patient was discharged after 2 weeks of inpatient stay with folic acid supplementation and iron chelating agent with a plan to do clinical exome sequencing. Upon discharge, except for her hemoglobin (8.8 g/dl) the WBC and platelet count normalized with improvement of total bilirubin 2.844 mg/dl and direct bilirubin 1.589 mg/dl.

Clinical exome-sequencing demonstrated a heterozygous variant of c.2863C > T (p.Arg955Ter) in exon 16 of the *SPTB* (NM_001355436.2) gene on chromosome 14 (chr14: 65253820). This nonsense mutation has been previously described as pathogenic in Indian and Chinese patients [9, 10]. Hereditary spherocytosis was diagnosed, and family screening was advised.

During the follow-up, she had persistently icteric sclera and fatigue. Investigations showed a hemoglobin level of 8 (reference range 12.7–14.7) g/dl, MCHC of 38 (reference range 30–36) g/dl, RDW of 16% (reference range 12–15%), and indirect hyperbilirubinemia [total bilirubin 5.8 (reference range 0.2–1.2) mg/dl and direct bilirubin 0.9 (reference range 0–0.5) mg/dl]. Liver enzymes were normalized (AST 17 U/L, ALT 5 U/L, and ALP 43 U/L). After 2 weeks of 1 gm daily intramuscular deferoxamine injection, her iron profile improved, with her serum ferritin level falling to 255 ng/ml. Surgery was planned as a result of the ongoing anemia and hyperbilirubinemia.

Preoperative preparation was difficult because her hematocrit level was less than 21% despite three units of blood transfusion. Vaccinations for pneumococcus, *Haemophilus influenzae*, and meningococcus were provided. To decongest and minimize blood loss isolated hilar inferior pole arteries ligated during surgery and allowed 30 min for venous drainage. Meanwhile, a cholecystectomy was performed, followed by the ligation of the splenic veins and a resection of the spleen (Fig. 3). The spleen weighed 3 kg. On gross histopathological examination, it measured 29 × 19 × 8.5 cm and showed mostly necrotic background on microscopic examination.

At 1 month after the surgery, the patient showed a significant improvement in clinical symptoms with normalization of hemolysis markers, as evidenced by a hemoglobin level of 14.1 g/dl and total and direct bilirubin levels of 0.77 and 0.35 mg/dl, respectively.



Fig. 3 Postoperative specimen showing the patient's huge, notched spleen, weighed 3 kg (blue arrow), and multiple gall bladder stones (red arrow)

Discussion

Hereditary spherocytosis (HS) is a common cause of hereditary hemolytic anemia. It is characterized by anemia, jaundice, splenomegaly, and reticulocytosis. For the clinical diagnosis of HS with typical symptoms, molecular testing is not frequently required [1]. The patient in this case had predominantly elevated direct hyperbilirubinemia, pancytopenia at presentation, a normal reticulocyte count, and an absence of family history, making the diagnosis difficult.

Atypical presentation of HS with mixed hyperbilirubinemia has been reported in previous studies [4, 11, 12]. As the disease progresses, individuals with HS may experience transitory biliary obstruction brought on by gallstones and hepatocellular damage owing to aberrant bilirubin metabolism [4]. In addition to HS, the *SPTB* mutation has also been proposed to cause liver damage and cirrhosis in adults [5] and pediatrics [6]. This case had a long-standing undetected disease and an *SPTB* gene mutation, but on follow up her bilirubin became

predominantly indirect with normal liver enzymes. Possible reasons for hepatocellular injury might be owing to the transient process and the sepsis.

Although absent reticulocytosis is uncommon in hereditary spherocytosis, it can occur when complicated by megaloblastic and aplastic crises, conditions typically associated with impaired reticulocyte response and often triggered by infections, including human parvovirus B19 as a common precipitant for aplastic crises [2]. Our patient displayed transient pancytopenia and suspicious megaloblastic features on peripheral morphology, likely indicative of a megaloblastic crisis. However, bone marrow evaluation and serologic testing for human parvovirus B19 were not performed. Furthermore, the reticulocyte count test was done 2 weeks following the blood transfusion, therefore an improvement in oxygenation possibly contributed to the unexpected reticulocyte count. Similarly, previous case reports have demonstrated normal reticulocyte counts in hereditary spherocytosis with complications [13, 14], and following blood transfusion [15]. The reticulocyte count is a valuable, cheap, and quick initial step in the evaluation of anemia, and its omission, as in our case, can lead to delays in recognition of hemolytic anemias. Thus, clinical judgment and interpretation of laboratory results on the basis of clinical context are crucial.

In patients with unexplained intermittent jaundice and splenomegaly, particularly complicated by cholelithiasis, thorough diagnostic evaluations for all potential causes of acquired and hereditary hemolytic anemia are essential. Routine tests, such as elevated MCHC, RDW, and spherocytes on the peripheral smear, as seen in our case, suggest Hereditary Spherocytosis. Diagnostic tests for HS include the osmotic fragility test, EMA binding assay, osmotic gradient ektacytometry, and glycerol lysis test, each with variable sensitivity and specificity. The diagnostic yield increases when these tests are combined. However, with atypical clinical features and recent blood transfusion that confound other conventional diagnostic tests owing to mixed blood cell populations, as in our case, genetic testing became mandatory for a definitive diagnosis [12, 16].

Owing to its clinical similarity with HS and the features of a normal reticulocyte count and absence of family history, as seen in our patient despite the presence of an extended family, congenital dyserythropoietic anemia (CDA type 2) was our top differential diagnosis. The OGT and EMA binding tests can yield positive results in both conditions, necessitating genetic testing for accurate diagnosis [3, 17]. Furthermore, considering the patient's fatigue from frequent hospital visits and workups, along with the therapeutic implications, and the limited availability of all diagnostic tests locally requiring abroad referrals, where sample handling and transport could affect test accuracy, it was decided to proceed with a genetic test.

Genetic testing also aids in treatment by excluding other hereditary hemolytic anemias, such as xerocytosis and stomatocytosis, which require the avoidance of splenectomy because of risks and lack of response. Splenectomy is the standard treatment for hereditary spherocytosis in patients with severe symptoms and complications, whereas supportive care is recommended for those with mild illness [3, 18]. Although cholecystectomy in asymptomatic patients is controversial, our patient had simultaneous splenectomy and cholecystectomy to avoid complications due to multiple gallstones.

To the authors' knowledge, this is the first case report of genetically confirmed hereditary spherocytosis from Ethiopia where a delay in diagnosis has resulted in several complications, such as massive splenomegaly, cholelithiasis, and pulmonary hypertension. Additionally, the misdiagnosis has also led to the prescription of ferrous sulfate, which can amplify secondary iron overload that could result from the underlying illness. Because family members are scattered across the country, screening tests were not conducted. Therefore, it remains uncertain whether the condition is owing to autosomal dominant inheritance or a *de novo* mutation.

Conclusion

Hereditary spherocytosis exists in our country even though it is a rare disease. A strong clinical suspicion with meticulous review of the patient's medical history and physical examination is necessary for early diagnosis and prevention of complications. Hereditary spherocytosis should be considered, and appropriate diagnostic procedures should be followed in patients presenting with anemia, jaundice, splenomegaly, and cholelithiasis. The diagnostic importance of routine laboratory testing, particularly reticulocyte count, MCHC, RDW, and peripheral smear, in hereditary spherocytosis, must not be overlooked. Genetic testing is crucial for confirming the diagnosis in cases with atypical presentations and confounding factors, such as recent blood transfusion, and it is valuable when planning surgical treatment to exclude conditions where splenectomy may not be safe or effective.

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Author contributions

SM and DeA did the evaluation, investigation, medical care, and follow-up; BS and TK handled the surgical management and follow-up; SM drafted the manuscript; DeA, AB, DaA, and ET took part in reviewing and editing the manuscript; HF created the figures. Before submission, all authors thoroughly examined and approved the paper.

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Availability of data and materials
We share the data upon request.

Declarations

Ethical approval
Ethical approval from the affiliated institution is not required for a single case report.

Consent for publication
Written informed consent was obtained from the patient for the publication of this case report and any accompanying images. A copy of written consent is available for review by the Editor-in-Chief of this journal.

Conflict of interest
The authors have no relevant conflicts of interest.

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