Letter to the Editor

Glucose-6-phosphate isomerase deficiency hemolysis

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Introduction

Glucose phosphate isomerase (GPI) deficiency (GPID), an autosomal recessive disorder, is considered to be one of the most common types of erythro-enzymopathy of anaerobic glycolysis (1). Here, we report a case of GPI double heterozygous mutation, which was diagnosed with DNA sequencing when treating cholecystolithiasis and choledocholithiasis. This case highlights the importance of accurately diagnosing glucose-6-phosphate isomerase hemolysis in patients with icterus.

Case presentation

All procedures performed in this study were in accordance with the ethical standards of the relevant institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

A 22-year-old woman was admitted to the general surgery department with cholecystolithiasis, cholecystitis, and choledocholithiasis. When she was only 3 days old, she had developed yellow staining of the sclera. At that time, she was diagnosed with congenital hemolysis, which was improved after conservative treatment. Since then, she has had jaundice without other discomfort and no further treatment. In April 2021, gallbladder stones and splenomegaly were found during physical examination. The surgeon thought it was secondary to congenital hemolysis and suggested consulting a hematologist. In May 2021, the hematologist performed red blood cell disease DNA sequencing, and the result was missense mutations in GPI exon 4 (c.286C>T, p.Arg96X; c.301G>A, p.Val101Met), which confirmed the diagnosis of GPID. The hematologist recommended splenectomy and cholecystectomy. The patient did not take this advice until December 2021, when she began to develop right upper abdominal pain after eating, accompanied by vomiting and diarrhea. It has since occurred 3 times, each time without fever, chills, tarry stool, or white stool change. The surgeon's examination revealed cholecystolithiasis, acute cholecystitis, and the presence of common hepatic duct calculi. In June 2022, the patient decided to adopt surgical treatment. In the preoperative examination, color ultrasound and enhanced computed tomography suggested multiple gallstones in the gallbladder and chronic cholecystitis. A calculus at the proximal end of the common bile duct was 2.2 cm × 1.0 cm in size, and the width of the distal common bile duct was 0.4 cm. Laboratory examination showed the following measures: red blood cell 2.62×10^{12}/L, hemoglobin 97 g/L, white blood cell 3.43×10^{9}/L, platelet 203×10^{9}/L, alanine aminotransferase 21 U/L, total bilirubin 181.5 μmol/L, and direct bilirubin 14.5 μmol/L. A peripheral blood smear showed that the red blood cells were significantly deformed and shrunken and indicated the following features of hemolysis: anemia with marked

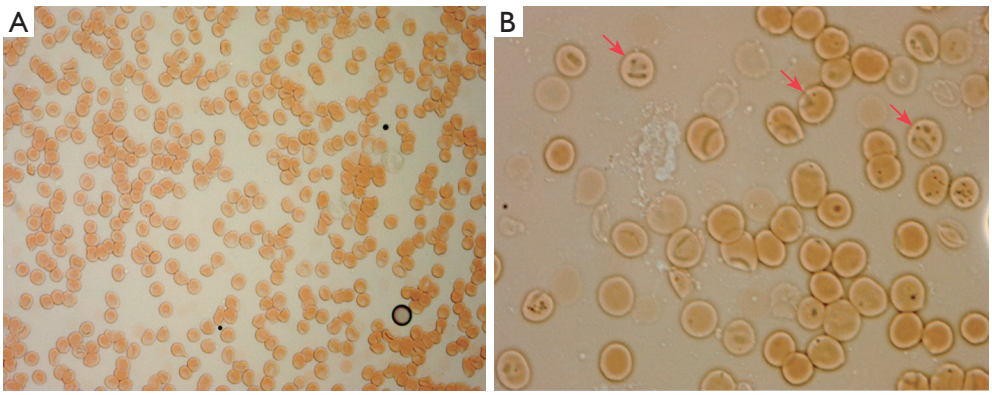

Figure 1 Appearance of blood cells in a hemolytic patient with glucose-6-phosphate isomerase deficiency under light microscopy with conventional Wright's stain. Red arrows indicate red blood cells containing denatured hemoglobin with an "emoji"-like appearance. (A) Eyepiece 10×, objective 40×. (B) Eyepiece 10×, objective 100×.

anisopoikilocytosis including occasional blister cells and bite cells, with some cells containing denatured hemoglobin with an "emoji"-like appearance (*Figure 1*, red arrows). She underwent laparoscopic splenectomy, cholecystectomy, choledocholithotomy, and T-tube drainage on June 27, 2022. Prophylactic antibiotics were used before and after surgery, and no explosive infection was found after surgery. The patient recovered and was discharged on the ninth day after surgery. The laboratory tests at discharge indicated the following measures: red blood cell 2.81×10^{12}/L, hemoglobin 92 g/L, white blood cell 10.63×10^{9}/L, platelet $1,209\times10^{9}$/L, alanine aminotransferase 73 U/L, total bilirubin 87.4 μmol/L, and direct bilirubin 14.8 μmol/L. Hematologists believed that there was no clear evidence that antiplatelet therapy could benefit patients with GPID after splenectomy, and the patient had no history of thrombosis, hypertension, diabetes, hyperlipidemia, or other high-risk factors. It was recommended to closely monitor blood routine. At the time of writing, we have followed her up for 1 year after the surgery. The patient's condition is stable, there is no significant hemolysis, the number of blood transfusions has been significantly reduced, and the hemoglobin level is around 100 g/L.

Discussion

GPID was first reported by Baughan in 1968 (2), and since then there have been about 60 cases reported from different races and populations. The gene locus encoding GPI is located on chromosome 19q13.1 and contains 18 exons, with its complement DNA (cDNA) of 1.9 kb codes for 558 amino acids (3). To date, a total of 57 GPI pathogenic variants have been reported at the molecular level, which includes 53 missense/nonsense, 1 splicing, and 3 small deletions. It does not seem that the type or location of mutations correlate with disease severity (4).

Chronic nonspherocytic hemolytic anemia (CNSHA) often affects patients with GPID to variable severities. The major clinical features of hemolysis include variable degrees of jaundice, slight-to-moderate splenomegaly, an increased incidence of gallstones, and anemia. A few reported cases with neuromuscular symptoms or intellectual disability have been reported (5,6). Some patients die at birth or even during the fetal period (6,7). In patients with hemolysis, red blood cell morphology is characterized by anisocytosis, poikilocytosis, polychromatophilia, and often nucleation. The blister cells and bite cells, which we describe as "emoji cells", have been reported in patients with glucose-6-phosphate isomerase deficiency (G6PD) (8). The bite cells are red blood cells with one or more arched defects at the edge of the cell, and the missing part is caused by the removal of denatured hemoglobin by macrophages in the spleen. G6PD leads to hemoglobin denaturation and the formation of Heinz bodies under uncontrolled oxidative stress. After the Heinz bodies are cleared by the spleen, one or more red blood cells with arc gaps appear in the cytoplasm. The hemoglobin in blister cells, usually the precursor of bite mark cell cells, contracts to form half a dense clump, while the remaining part appears in the form of hollow red blood cells. In some complex cases, the combined deficiency of GPI and G6PD may lead to a totally different clinical outcome (4,9), making the diagnostic process more difficult.

For patients with CNSHA, the main diagnostic method

is to exclude other common causes of congenital hemolytic anemia, confirm a decrease in GPI enzyme activity in red blood cells, and make a diagnosis through GPI gene mutation analysis (4). In short, diagnosis is made via documenting decreased red blood cell GPI activity on an enzymatic assay or via detecting pathogenic variants of GPI in genetic testing (3). However, due to the lack of knowledge concerning a few rare disorders and the availability of the enzymatic assay, a definitive diagnosis is often elusive (10,11). Moreover, the determination of enzyme activity is easily influenced by various factors, and there is no clear correlation between the severity of anemia in patients, enzyme activity, and genotype. Therefore, genetic diagnosis is currently the most accurate method for diagnosing this disease. Moreover, targeted next-generation sequencing (NGS) can enable the detection of specific congenital haemolytic anaemia (CHA) mutations, which is valuable for the diagnosis of unexplained hemolytic anemia (10). Although our center lacks the availability to conduct enzymatic assay, we performed targeted NGS for this patient, which indicated that both GPI variants were deleterious mutations. The two mutations were both missense mutations in GPI exon 4 (c.286C >T, p.Arg96X; c.301G>A, p.Val101Met), located in a hotspot mutation region, which has been reported previously in the literature (1,3).

There is no specific treatment for GPID. Transfusion-dependent patients can benefit from splenectomy (3), which may increase thrombotic risk. Other symptomatic treatments included fluid infusion, blood transfusions, prevention of infections, monitoring for gallstones, avoiding oxidant exposures, and the use of folic acid. Park *et al.* reported a patient with GPID, CNSHA, and intractable seizures who demonstrated a dramatic resolution of seizures and reduction in hemolysis and transfusion dependence following initiation of a ketogenic diet (12). Iron overload often occurs in common glycolytic enzymopathies, including hyperhemolysis or ineffective erythropoiesis. However, information on iron status in GPID is scant. It may be that monitoring of iron status may be valuable in managing this disease.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-22-1154/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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