Gilbert syndrome with systemic lupus erythematosus presenting with persistent unconjugated hyperbilirubinemia: A case report

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Abstract. Gilbert syndrome (GS) is a hereditary unconjugated hyperbilirubinemia that results from mutations in the bilirubin uridine diphosphate-glucuronosyltransferase (UGT1A1) gene. To the best of our knowledge, there are currently no reports that focus on patients with systemic lupus erythematosus (SLE) coexisting with GS. The present study aimed to evaluate the clinical characteristics and genotype of UGT1A1 in a Chinese patient with SLE and GS. Complete medical records and laboratory data were reviewed for a patient with SLE referred to Ruijin Hospital (Shanghai, China) for treatment between March 2016 and January 2020. Genetic analysis of the UGT1A1 gene was performed by PCR amplification and Sanger sequencing. The serum total bilirubin and unconjugated bilirubin concentrations on admission were 96.2 and 86.8 µmol/l, respectively. The homozygous mutation c.1456T>G (p.Y486D) in exon 5 was detected in this patient. The patient had a good response to phenobarbital orally at a dose of 30 mg/day and a decrease in serum bilirubin was observed. Elevated unconjugated hyperbilirubinemia in SLE needs to be differentiated from other diseases, such as GS, which can be diagnosed by UGT1A1 genetic sequencing.

Introduction

Gilbert syndrome (GS) is a common autosomal dominant disorder that results in intermittent hyperbilirubinemia in the absence of any signs or symptoms of liver disease (1). GS usually manifests in decreased activity of the uridine diphosphate-glucuronosyltransferase (UGT1A1) gene with an incidence of ~5-10% in the global population from 2018 (1,2). UGT1A1 gene encodes a UDP-glucuronosyltransferase, which transforms small lipophilic molecules, including bilirubin into water-soluble, excretable metabolites. Several variations in the UGT1A1 gene have been described, including UGT1A1*28, UGT1A1*60 and UGT1A1*93 (3,4). GS in combination with diseases, such as thalassemia, glucose-6-phosphate dehydrogenase (G6PD) deficiency, spherocytosis and acute lymphoblastic leukemia may potentiate severe hyperbilirubinemia (5-9). In addition, GS may decrease plasma oxidation and affect drug metabolism, such as irinotecan hydrochloride by decreasing the ability to conjugate drugs (10). However, to the best of our knowledge, there are currently no reports about patients with systemic lupus erythematosus (SLE) coexisting with GS. SLE is a chronic multisystem inflammatory disease characterized by the production of various autoantibodies, such as anti-double-stranded DNA antibodies (anti-dsDNA antibodies), anti-Sm antibodies and anti-SSA/SSB antibodies. Fang et al (11) indicated that hepatic manifestation triggered by SLE itself is controversial and usually asymptomatic. This is due to the fact a variety of causes need to be differentiated, such as i) an overlap of SLE with autoimmune hepatitis (AIH) or primary biliary cirrhosis; ii) an overlap of SLE with non-autoimmune hepatopathy; iii) the existence of liver injury that only relates to SLE. And elevated liver parameters seem to be common, accounting for 25-50% patients with SLE (11); however, the etiology of hepatic damage remains unclear (12). A study by Vitek et al (13) that involved 259 patients with SLE revealed that SLE disease activity was accompanied by very low serum bilirubin levels, which were caused by severe oxidative stress. Patients with GS may be protected from the development of SLE. The present study aimed to summarize the clinical characteristics, genetic type and treatment of a patient with SLE coexisting with GS.

Materials and methods

Patient characteristics, examination and treatment. A 27-year-old Chinese female patient was referred to Ruijin...
Hospita (Shanghai, China) displaying jaundice in March 2016. The jaundice began 6 years prior to admis- 
sion. The patients parents did not have jaundice, and she denied the use of potential cholestasis-inducing medica-
tion. The patient presented with a malar rash, arthritis, 
thrombocytopenia and decreased hemoglobin, but without 
kidney and nervous system involvement. The patient had 
no symptoms of photosensitivity, alopecia or oral ulcers. 
Autoantibody testing revealed that the patient had a titer 
of 1:100 for antinuclear antibody and that anti-Sjogren's 
syndrome A and B antibodies were positive as well. On 
this basis, the patient was diagnosed with SLE according 
to the 2011 classification criteria of the Systemic Lupus 
International Collaborating Clinics (14). The patient's 
laboratory findings were as follows: Hemoglobin, 80 g/l 
(reference value: 110-150 g/l); white blood cell count, 
9.0×10^9/l (reference value: 4.0-10.0×10^9/l); and platelet 
(PLT) count, 50.0×10^9/l (reference value: 100-300×10^9/l). 
The liver function test revealed that serum levels of aspar-
tate aminotransferase, alanine aminotransferase, alkaline 
phosphatase and γ-glutamyl transpeptidase were normal 
and total bilirubin (TB) was 91.1 µmol/l (3.4-20.5 µmol/l), 
and direct bilirubin (DB) was 12.5 µmol/l (0.0-6.8 µmol/l). 
Therefore, the patient was characterized with persistent 
elevated indirect (unconjugated) bilirubin (IB). For the 
immunosuppressive therapy, hydroxychloroquine at a dose 
of 200 mg twice/day, prednisone 40 mg/day and cyclospor 
in a 21-month-old girl with unconjugated hyperbilirubinemia. 
the (TA)6TAA box and the missense mutation (G 

PCR amplification and sequencing. A total of 2 ml patient 
peripheral blood was collected in a tube containing ethylene-
diaminetetraacetic acid (EDTA). Genomic DNA was extracted 
from the peripheral blood sample using the membrane-based 
QiAamp DNA extraction kit (Qiagen GmbH) according 
to the manufacturer's instructions. DNA concentration and 
purity were measured with a spectrophotometer (NanoDrop 
2000; Thermo Fisher Scientific, Inc.). Primer pairs were the 
same as used in a previous study (15). The promoter, exons 
1-5, adjacent intronic regions and the phenobarbital response 
enhancer module of the UGT1A1 gene were analyzed by 
polymerase chain reaction (PCR). PCR mixtures were initially 
denatured at 95°C for 5 min, followed by 35 cycles of 30 sec 
95°C denaturation, 30 sec 54-64°C annealing according 
to the primer pair being used and 45 sec extension at 72°C, with 
a final extension at 72 for 10 min. PCR products (5 µl) were 
sequenced with the Big-Dye Terminator Sequencing kit and 
an ABI 377 automated DNA sequencer (Applied Biosystems, 
Thermo Fisher Scientific Inc.).

Follow-ups. The follow-up of this patient including clinical 
symptoms, signs and laboratory examinations, such as ESR, 
PLT, liver function tests was conducted every 1 to 3 months. In 
addition, the SLEDAI score was evaluated each time (16,17). 
The total follow-up period was 46 months.

Results

Laboratory data and treatment. Laboratory data were 
recorded consecutively and were presented in Table I. TB, 
IB and ESR levels were elevated at admission. Then, TB and 
IB levels remained stable from June 2016 to October 2016. 
Treatment using phenobarbital at a dose of 30 mg/day was 
started on November 4, 2016 until November 10, 2016.

Mutation in the UGT1A1 gene. A direct sequencing analysis 
was conducted to identify the mutation in the UGT1A1 gene 
of the patient. The analysis revealed a homozygous mutation 
from a T to G at nucleotide position 1456 in UGT1A1 
exon 5 (c.1456T>G), resulting in the substitution of aspar-
tate to tyrosine at position 486 of the UGT1A1 protein 
(p.Y486D) (Fig. 1).

Outcome and follow-up period. SLE activity indicators, such 
as ESR, high-sensitivity C-reactive protein and anti-dsDNA 
antibody remained normal during the follow-up period. 
SLEDAI score varied from 0 to 1. Following phenobarbital 
treatment for 1 week, there was a rapid decrease in bilirubin 
levels (Fig. 2). TB and IB were decreased and therapy was 
well tolerated without any side effects. After 46 months of 
follow up, the patient remained stable on low-dose oral predni-
sone (10 mg/day) and cyclosporin (50 mg twice/day). The latest 
TB and IB values were 81.5 and 71.7 µmol/l, respecti-
vely (Table I).

Discussion

GS is caused by a mutation in the UGT1A1 gene resulting 
in impairment of glucuronidation of unconjugated bilirubin 
within hepatocytes. Several studies have reported the coexis-
tence of GS and hereditary spherocytosis, G6PD deficiency, 
galstone disease and other diseases (8,18,19). The reports 
were summarized in Table II for UGT1A1 genetic mutations 
and related diseases during the past 4 years. Butorac et al (7) 
reported the coexistence of hereditary spherocytosis and GS 
in a 21-month-old girl with unconjugated hyperbilirubinemia. 
Li et al (20) reported the combination of myeloprolifera-
tive neoplasms and the presence of the insertion mutation with 
the (TA)6TAA box and the missense mutation (G→A) 
at 211 bp of exon 1 in the UGT1A1 gene. Recently, over 130 
genetic variants in the UGT1A1 gene were associated with 
GS after assessing the presence of genetic polymorphisms 
among different ethnicities (21). East Asian individuals had a 
prevalence of ~2% for the genetic variants in the UGT1A1 
gene, while Caucasian individuals had a prevalence of 
2-10%, and Southern Asian and Middle Eastern indi-
viduals demonstrated a significantly increased prevalence of 
20% (22-24). A TA insertion mutation in the TATA box 
[A (TA) 7TAA] (UGT1A1*28) and c0.211 G>A (p.G71R) 
in exon 1 (UGT1A1*6) were common (25-27). A(TA)7TAA
was the most common mutation in the UGT1A1 gene seen in Caucasian individuals, accounting for ~35-40% (28). A study from a Romanian cohort demonstrated that the polymorphism with the highest frequency was the UGT1A1 7TA (UGT1A1*28) (29). However, a Chinese study revealed that 36.3% of patients with GS had the c.3279T>G mutation (30). And the frequency of A (TA) 7TAA was 30.6%, which was lower compared with Caucasians (21). To the best of our knowledge, the present study demonstrated the first patient diagnosed as SLE with GS who had the homozygous mutation c.1456 T>G (p.Y486D) in the UGT1A1 gene. The patient in the present study presented with persistent unconjugated hyperbilirubinemia and had a good response to phenobarbital with a decrease in bilirubin, which confirmed the diagnosis of GS. Low-dose phenobarbital can be used continuously in patients with GS who tolerate it well. During the 46 month follow-up period, the patient exhibited stable SLE activity and serum bilirubin level. A limitation of the present study was lack of family gene verification, as the parents of the patient did not have jaundice and refused gene testing.

Nakagawa et al (31) described a single homozygote for the p.Y486D mutation in UGT1A1 exon 5, one of the shared exons, and predicted that the p.Y486D mutation may disturb the metabolization of the antipyretic and acetaminophen. This may affect the activity of the UGT1A1, UGT1A6 and UGT1A9 genes, which catalyze acetaminophen glucuronidation (32). Acetaminophen (~85%) is metabolized by conjugation, mainly glucuronidation through UDP-glucuronosyltransferase (33). Ha et al (10) revealed that UGT1A1 genetic polymorphisms, particularly the UGT1A1*28 allele of GS may alter the metabolism of drugs, such as irinotecan hydrochloride by decreasing the ability to conjugate drugs. Attention should be paid to the use of these drugs in patients with GS.

The coexistence of SLE and GS requires further investigation. The association between serum bilirubin and SLE activity remains unclear. Serum bilirubin is the final product of hemoglobin metabolism (34). Severe hyperbilirubinemia could lead to cholestasis and neurological impairments (neurotoxicity or kernicterus), which have considerable morbidity and mortality risks (35). It was revealed that bilirubin has potent cytoprotective action due to its anti-inflammatory, anti-oxidant and immunosuppressive roles at low concentrations, and mild hyperbilirubinemia prevents the development of ischemic heart disease by increasing the serum antioxidant capacity (36-39). Patients with GS had low levels of oxidative stress associated with hyperbilirubinemia (40). In addition, GS was associated with a decreased prevalence of cardiovascular disease, diabetes, endometrial cancers and with a better prognosis for Hodgkin's lymphoma (1,39,41-43). In the present study, unconjugated bilirubin levels were elevated, while the SLE activity indicators remained normal and stable, such as the SLEDAI score. dos Santos et al (44) reported that unconjugated bilirubin level in SLE was negatively correlated with disease activity, which is consistent with the present study. Although the activity of SLE increases oxidative stress, serum bilirubin

Table I. Variation of laboratory data during follow-ups for the patient with systematic lupus erythematosus and coexisting Gilbert syndrome.

| Time, day/month/year | ESR, mm/h | PLT, x10^9/l | TB, µmol/l | DB, µmol/l | IB, µmol/l |
|----------------------|-----------|--------------|------------|-------------|------------|
| 28/03/2016           | 23        | 106          | 96.2       | 9.4         | 86.8       |
| 29/06/2016           | 9         | 108          | 87.2       | 11.4        | 75.8       |
| 19/07/2016           | 13        | 90           | 90.7       | 10.5        | 80.2       |
| 10/08/2016           | 5         | 88           | 89.5       | 12.4        | 77.1       |
| 11/10/2016           | 6         | 75           | 90.7       | 10.5        | 80.2       |
| 04/11/2016           | 8         | 54           | 77.2       | 8.7         | 68.5       |
| 10/11/2016           | 7         | 50           | 54.2       | 8.9         | 45.3       |
| 29/11/2017           | 22        | 15           | 80.2       | 9.0         | 71.2       |
| 30/05/2018           | 7         | 43           | 66.5       | 8.8         | 57.7       |
| 01/03/2019           | 13        | 27           | 67.6       | 9.1         | 58.5       |
| 06/01/2020           | 12        | 32           | 81.5       | 9.8         | 71.7       |

ESR, erythrocyte sedimentation rate; PLT, platelet; TB, total bilirubin; DB, direct bilirubin; IB, indirect bilirubin.

Figure 1. Mutation in the UGT1A1 gene in the patient. Sequencing analysis revealed a homozygous mutation from a T to G at nucleotide position 1456 in UGT1A1 exon 5 (c.1456T>G), resulting in the substitution of aspartate for tyrosine at position 486 of the UGT1A1 protein (p.Y486D). Tyr, tyrosine; Asp, aspartate.
plays an important role in controlling it (45). Patients with GS can be treated with phenobarbital or no medication. When a patient experiences any other factors, such as menstruation, infection, surgery or overexertion, the degree of jaundice could be aggravated.

To conclude, the present study identified a homozygous mutation, c.1456T>G, in a patient with SLE with persistent hyperbilirubinemia coexisting with GS. It is pivotal that elevated unconjugated hyperbilirubinemia in SLE should be differentiated from other diseases, such as GS.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article.

Authors’ contributions

NY and ZZ drafted the manuscript. HG performed the laboratory tests. YH performed the PCR amplification and

Table II. UGT1A1 genetic mutations and related diseases during the 4 year follow up period.

| First author, year | Number of patients | Country | Disease | Mutations (Refs.) |
|-------------------|--------------------|---------|---------|------------------|
| Maruo, et al 2016 | 121                | Japan   | GS      | p.G71R,p.P229Q, c.-3279T>G:A(TA)7TAA (3) |
| Jamwal, et al 2016| 3                  | India   | GS, G6PD-deficiency, HS (TA)_77 repeats (46) |
| Singer, et al 2016| 43                 | Israel  | GS, type I diabetes Not mentioned (47) |
| Radoi, et al 2017 | 292                | Romania | GS      | UGT1A1 (7TA), UGT1A1 (8TA) (29) |
| Moyer, et al 2017 | 54                 | England | GS, neonatal jaundice Novel variants: c.337T>G (p.Y113D), c.1469A>C(p.D490A) (48) |
| Li, et al 2017    | 1                  | China   | GS, MPN (TA)6TAA, c.-211G>A (20) |
| Sun, et al 2017   | 59                 | China   | GS      | c.-3279T>G, A(TA)_7TAA, p.G71R, p.P229Q, p.P364L, p.Y486D (30) |
| Aiso, et al 2017  | 1                  | Japan   | GS, HS  | A(TA), TAA, c.211G>A:p.G71R (49) |
| Pasha, et al 2017 | 51                 | Iran    | GS      | UGT1A1 (7TA) (50) |
| Haddad, et al 2017| 1                  | Tunisia | GS, β-thalassemia (TA)_(TA)_7 (51) |
| Butorac, et al 2018| 1                 | Croatia | GS, HS  | UGT1A1 (7TA) (7) |
| Qian, et al 2018  | 1                  | China   | GS, gallstone disease A(TA), TAA, c.-364C>T, c.-1352A>C (52) |
| Bale, et al 2018  | 1,191              | India   | GS, gallstone disease UGT1A1(TA)n (19) |
| Kamal, et al 2019 | 110                | Egypt   | GS      | A(TA), TAA (53) |

GS, Gilbert syndrome; G6PD-deficiency, glucose-6-phosphate dehydrogenase deficiency; HS, hereditary spherocytosis; MPN, myeloproliferative neoplasm; ALL, acute lymphoblastic leukemia.

Figure 2. Variations in serum bilirubin during follow up. The figure presents the variations in serum bilirubin during follow up. The patient was treated with phenobarbital on November 4, 2016. After 1 week, there was a rapid decrease in total and indirect bilirubin levels. TB, total bilirubin; DB, direct bilirubin; IB, indirect bilirubin.
The authors declare that they have no competing interests.

**Patient consent for publication**

The patient referred to in this study provided consent for the publication of this study. JT performed the follow-up task and analysed the data. The present study was approved by the Ethics Committee of Ruijin Hospital (ID: 2016-62) and signed informed consent was obtained from the patient.

**Compiling interests**

The authors declare that they have no competing interests.

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