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

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Received November 26, 2019; Accepted June 3, 2020

DOI: 10.3892/etm.2020.9219

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

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Key words: systemic lupus erythematosus, Gilbert syndrome, genotype, hyperbilirubinemia

Hospital (Shanghai, China) displaying jaundice in March 2016. The jaundice began 6 years prior to admission. The patients parents did not have jaundice, and she denied the use of potential cholestasis-inducing medication. 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, $9.0x10^9$/l (reference value: 4.0-10.0$x10^9$/l); and platelet (PLT) count, 50.0$x10^9$/l (reference value: 100-300$x10^9$/l). The liver function test revealed that serum levels of aspartate 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 cyclosporine 50 mg twice/day orally were used. The patient was in a stable condition with regard to the SLE disease activity. However, jaundice still existed. TB, DB, erythrocyte sedimentation rate (ESR) and PLT were detected in Ruijin Hospital (Shanghai, China), consecutively. The Coombs test was negative, which excluded hemolytic anemia. Transaminases and serological tests for hepatitis B and C were negative, which excluded virus hepatitis. There was no obvious abnormality on the abdominal ultrasound or bone marrow biopsy. Informed written consent and consent for publication were obtained from the patient. This study was approved by the Ethics Committee of Ruijin Hospital (ID: 2016-62).

PCR amplification and sequencing. A total of 2 ml patient peripheral blood was collected in a tube containing ethylenediaminetetraacetic 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 aspartate 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 prednisone (10 mg/day) and cyclosporin (50 mg twice/day). The latest TB and IB values were 81.5 and 71.7 μmol/l, respectively (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 coexistence of GS and hereditary spherocytosis, G6PD deficiency, gallstone 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 myeloproliferative 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 individuals 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

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.

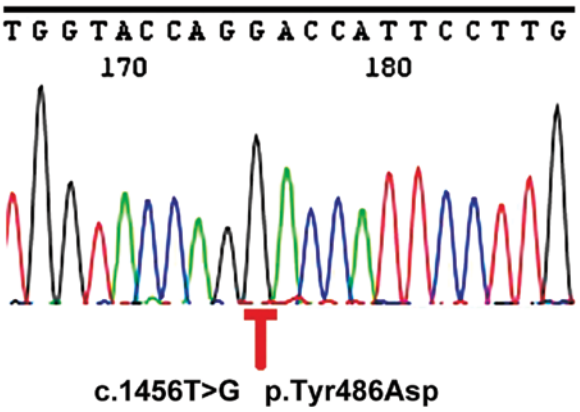

Figure 1. Mutation in the UGT1A1 gene in the patient. Sequencing analysis revealed a homozygous mutation from a T to G at nucleotide position 1456 in UGT1A1 exon 5 (c.1456T>G), resulting in the substitution of aspartate for tyrosine at position 486 of the UGT1A1 protein (p.Y486D). Tyr, tyrosine; Asp, aspartate.

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-glucuro nosyltransferase (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 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	$(TA)_{7/7}$ 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	$A(TA)_7TAA$, 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	$(TA)_6/(TA)_7$	(51)
Butorac, *et al* 2018	1	Croatia	GS, HS	UGT1A1 (7TA)	(7)
Qian, *et al* 2018	1	China	GS, gallstone disease	$A(TA)_7TAA$, 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	$A(TA)_7TAA$	(53)

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

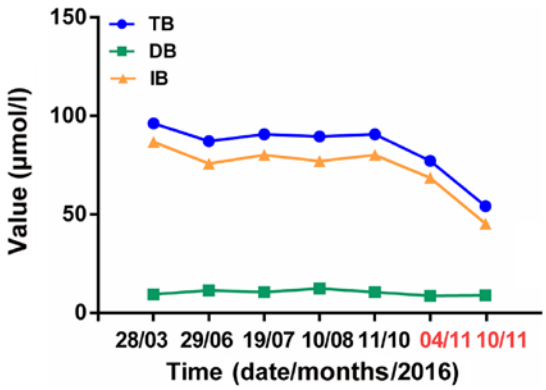

Figure 2. Variations in serum bilirubin during follow up. The figure presents the variations in serum bilirubin during follow up. The patient was treated with phenobarbital on November 4, 2016. After 1 week, there was a rapid decrease in total and indirect bilirubin levels. TB, total bilirubin; DB, direct bilirubin; IB, indirect bilirubin.

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.

Acknowledgements

Not applicable.

Funding

The present study was supported by grants from the National Natural Science Foundation of China (grant no. 81801592), Shanghai Sailing Program (grant no. 18YF1414100), and Excellent Youth B Project (grant no. GCQN-2017-B05) and Innovative Research Team of high-level local universities in Shanghai.

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

sequencing. JT performed the follow-up task and analysed clinical data. The experiments were designed by JY and CY. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Ruijin Hospital (ID: 2016-62) and signed informed consent was obtained from the patient.

Patient consent for publication

The patient referred to in this study provided consent for the publication of her information.

Competing interests

The authors declare that they have no competing interests.

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