Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.8673-21
Intern Med 61: 1537-1543, 2022
http://internmed.jp

【 CASE REPORT 】

Chronic Infection with Hepatitis C Virus Subtype 1g in a Japanese Patient Successfully Treated with Glecaprevir/Pibrentasvir

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Abstract:
A 66-year-old man, who had undergone plasma exchange 30 years previously in Egypt for the treatment of falciparum malaria, was referred to our hospital for treatment of chronic hepatitis C (HCV). An analysis of the 655-nucleotide 5'-untranslated region-core region sequence revealed infection with HCV subtype 1g. A phylogenetic analysis of the full-length HCV genome confirmed that the patient's HCV was subtype 1g, which was the first case identified in Japan. Although his HCV possessed several naturally occurring resistance-associated substitutions in the nonstructural (NS)3 and NS5A regions, he was successfully treated by combination therapy with glecaprevir/pibrentasvir.

Key words: hepatitis C virus, subtype 1g, glecaprevir/pibrentasvir

(Intern Med 61: 1537-1543, 2022)
(DOI: 10.2169/internalmedicine.8673-21)

Introduction

Viral hepatitis is the seventh-most common leading cause of death worldwide, and hepatitis C virus (HCV) accounts for half of viral hepatitis-related mortality (1). Approximately 71 million individuals are estimated to be chronically infected with HCV globally (2). At present, HCV is classified into 8 distinct genotypes (3); the most frequent is genotype 1 (G1) (44%), followed by genotype 3 (G3) (25%), and genotype 4 (G4) (15%) (2). G1 dominates in high income and upper to middle income countries (accounting for approximately 60% of all infections in those countries), while G3 and G4 are common in lower-middle (accounting for 36%) and low income countries (accounting for 45%), respectively (2). Each genotype has ≥1 subtype, and there were 90 confirmed subtypes as of May 2019 (https://talk.ictvonline.org/ictv_wikis/flaviviridae/w/sg_flavi/56/hcv-classification). In Japan, the prevalence of subtypes 1b, 2a, and 2b is estimated to be 70%, 20%, and 10%, respectively (4). Recently, direct-acting antivirals (DAAs) for the treatment of hepatitis C have become available; these achieve a high cure rate with a short course of treatment. However, clinical trials (5-7) and real-world data (8-11) on the efficacy of DAAs have been reported exclusively from upper to middle income countries. Distinct subtypes of G1-

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Received: September 16, 2021; Accepted: October 27, 2021; Advance Publication by J-STAGE: December 11, 2021
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Table 1. Laboratory Findings.

Variables	Results	Variables	Results
WBC	5,800 /μL	UA	4.4 mg/dL
RBC	463×10⁴ /μL	Na	139 mEq/L
Hb	15.0 g/dL	K	5.0 mEq/L
Ht	44.1 %	Cl	104 mEq/L
Plt	33.2×10⁴ /μL	CRP	0.01 mg/dL
PT	127 %	Glucose	125 mg/dL
PT-INR	0.89	HbA1c	6.3 %
APTT	36.2 s	HBsAg	Negative
T.bil	0.66 mg/dL	HCVAb	Positive
D.bil	0.06 mg/dL	AFP	2.6 ng/mL
AST	24 U/L	AFP-L3	<0.5 %
ALT	28 U/L	DCP	28 mAUl/mL
LDH	156 U/L	TSH	2.6 μU/mL
ALP	98 U/L	fT3	2.85 pg/mL
γ-GT	25 U/L	fT4	0.99 ng/mL
TP	7.4 g/dL	FIB-4	0.90
Alb	4.3 g/dL	M2BPGi	0.67 C.O.I
T.chol	195 mg/dL	CAP	202 dB/m
TG	59 mg/dL	LSM	4.9 kPa
HDL-C	54 mg/dL	HCV-RNA	6.3 Log IU/mL
LDL-C	116 mg/dL	HCV grouping	1
BUN	13 mg/dL	HCV genotype	
Cr	0.72 mg/dL	Commercial base analysis	4
eGFR	83.5 mL/min/1.73 m²	Full genome analysis	1g

AFP: α-fetoprotein, AFP-L3: lens culinaris agglutinin-reactive fraction of α-fetoprotein, Alb: albumin, ALP: alkaline phosphatase, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, CAP: controlled attenuation parameter, Cr creatinine, CRP: C-reaction protein, D.bil: direct bilirubin, DCP: des-gamma-carboxy prothrombin, eGFR: estimated glomerular filtration rate, fT3: free triiodothyronine, fT4: free thyroxine, γ-GT: gamma-glutamyltransferase, Hb: hemoglobin, HBsAg: hepatitis B surface antigen, HCVAb: hepatitis C virus antibody, HDL-C: high-density lipoprotein cholesterol, Ht: hematocrit, LDH: lactate dehydrogenase, LDL-C: low-density lipoprotein cholesterol, LSM: liver stiffness measurement, M2BPGi: macrophage galactose-specific lectin-2 binding protein glycosylation isomer, PT: prothrombin time, PT-INR: prothrombin time international normalized ratio, RBC: red blood cell, RNA: ribonucleic acid, T.bil: total bilirubin, T.chol: total cholesterol, TG: triglyceride, TP: total protein, TSH: thyroid-stimulating hormone, UA: uric acid, WBC: white blood cell

G4 including G1 non-1a/1b, G2 non-2a/2b, G3 non-3a, and G4 non-4a/4d, as well as G5-G8, which are uncommon in Europe, North America, Australia, and Japan, have been reported to be highly prevalent in some regions of Africa and Asia (12). Data on the efficacy of DAA therapy are limited to patients living in these regions or immigrants from these regions.

We herein report the case of a Japanese patient who was infected with subtype 1g HCV in Egypt and who was successfully treated with glecaprevir/pibrentasvir (GLE/PIB), a pan-genotypic anti-HCV drug regimen. To our knowledge, this is the first report of a Japanese patient with subtype 1g HCV who was successfully treated with GLE/PIB.

Case Report

A 66-year-old man was referred to our hospital for the treatment of chronic hepatitis C infection. He had visited the Republic of Kenya at 36 years of age and developed falciparum malaria. He was admitted to a hospital in Egypt for two months and received intensive care, including plasma exchange treatment. His condition improved subsequently, and he returned to Japan. He later developed acute hepatitis due to HCV infection and was hospitalized for three months in a city hospital in Japan. He underwent interferon therapy 2 years after infection but failed to achieve HCV eradication. He had a history of receiving laparoscopic treatment for perforation of a duodenal ulcer three years previously, but did not undergo blood transfusion. He had no history of tattooing or drug abuse, and he had no family history of liver disease.

The laboratory findings before treatment are shown in Table 1. His platelet count was within the normal limit, and his hepatobiliary enzyme values were not elevated. HCV grouping was assigned to 1. Transient elastography (FibroScan; ECHOSENS, Paris, France) showed a controlled attenuation parameter of 202 dB/m and liver stiffness of 4.9 kPa. His HCV-ribonucleic acid (RNA) titer was 6.3 Log IU/

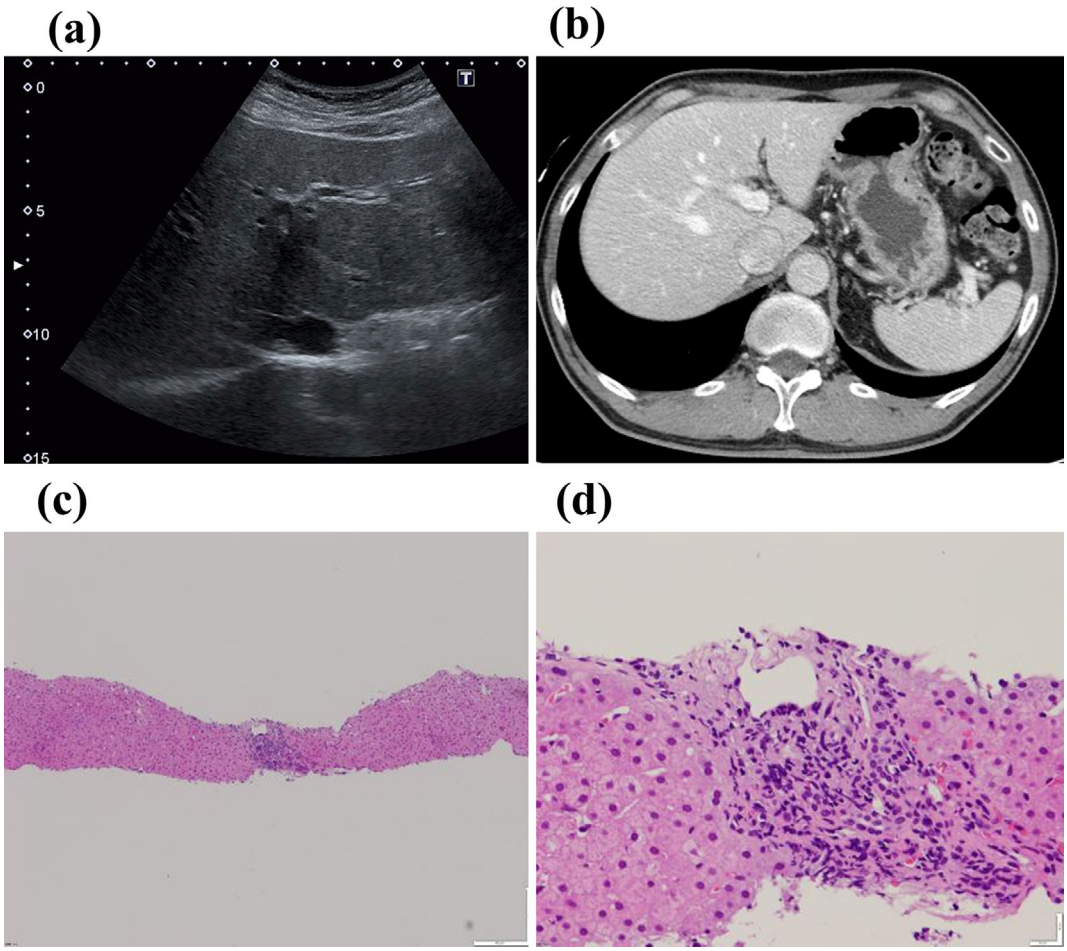

Figure 1. **(a) Ultrasonography showed a homogenous liver parenchyma and a smooth the liver surface, indicating chronic hepatitis. (b) Computed tomography (CT) also revealed chronic hepatitis and no findings of cirrhosis, such as collateral vein or splenomegaly. (c, d) The liver specimen showed that the hepatic lobule was preserved, and there was mild fibrosis, with scarce inflammatory cells in the limited portal vein area (A0F1).**

mL. According to the commercial base analysis of a short HCV 5'-untranslated region (UTR) sequence, his HCV genotype was determined to be G4 (not G1b, G2a, or G2b). Because HCV G4 is known to be endemic in Egypt (13, 14) and he had received transfusion in Egypt, we initially diagnosed him with HCV G4 infection. Abdominal ultrasonography (US) showed a homogenous liver parenchyma and a smooth liver surface, with no signs of liver cirrhosis (Fig. 1a). Computed tomography (CT) also revealed chronic hepatitis and no signs of cirrhosis, such as collateral veins or splenomegaly (Fig. 1b). No liver tumor mass was detected on US or CT. We performed a liver biopsy under ultrasound guidance, showing the preservation of the hepatic lobule and presence of mild fibrosis and scarce inflammatory cells in the limited portal vein area (A0F1; Fig. 1c, d). Following the acquisition of written informed consent from the patient, we started 12-week oral combination therapy with GLE (300 mg daily) and PIB (120 mg daily), according to the recommendation of the Japanese National Health Insurance system. There were no adverse events during treatment. Serum HCV-RNA was undetectable at 12 weeks after treatment; thus, the patient achieved a sustained virological response at 12 weeks (Fig. 2). To investigate the precise HCV subtypes, RNA was extracted from a frozen serum sample (HC21-0545) that had been stored before treatment, and nested reverse transcription polymerase chain reaction (RT-PCR) of the 655-nucleotide (nt) 5' UTR-core region sequence and direct sequencing of the amplicons were carried out according to the previously described method (15). Neighbor-joining trees of the Jukes-Cantor distances were produced with 1,000 replicates of bootstrap resampling, as implemented in the MEGA7 software program (version 7.0.26) (16). Surprisingly, the phylogenetic tree constructed based on the 655-nt 5' UTR-core region sequence indicated that the HC21-0545 strain is classifiable into subtype 1g within G1 (Fig. 3a). To confirm the HCV subtype, the entire genomic sequence of the HC21-0545 strain (9428 nt, excluding polyU tail) was determined by the previously described method (17) and subjected to the phylogenetic analysis. The tree confirmed that the HC21-0545 strain is segregated into the subtype 1g cluster, which consists of nine reported subtype 1g strains identified in Egypt,

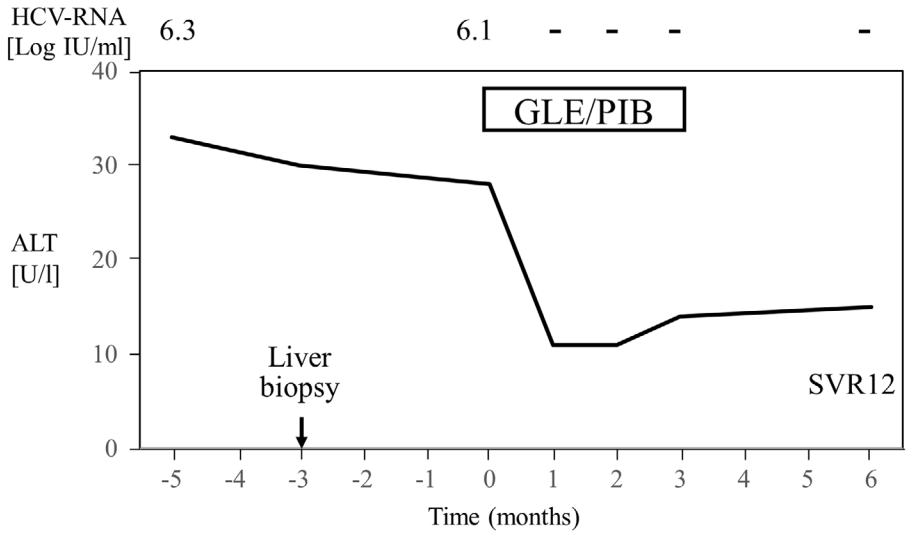

Figure 2. **Clinical course. ALT: alanine aminotransferase, GLE/PIB: glecaprevir/pibrentasvir, SVR12: sustained virological response at 12 weeks**

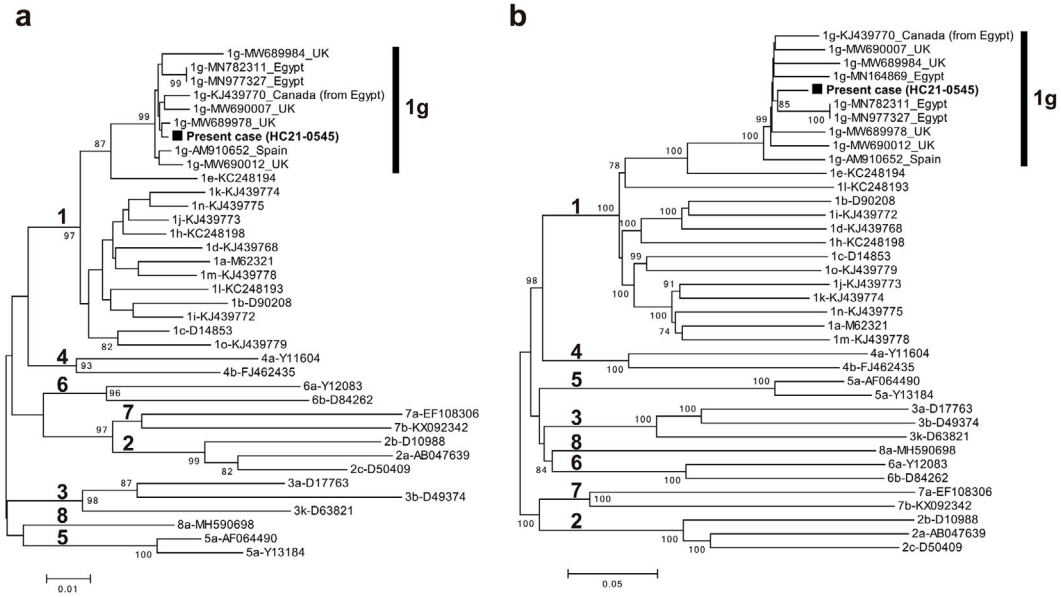

Figure 3. **Phylogenetic trees of the present case (HC21-0545) constructed based on the 655-nucleotide (nt) 5'-untranslated region (UTR)-core region sequence (a) and the entire genomic sequence (b). The HCV strain (HC21-0545) obtained in the present study is highlighted with a closed box and indicated with bold typeface. The reported HCV strains of G1-G8 are indicated with the subtype, followed by the DDBJ/EMBL/GenBank accession number and country where it was isolated (for subtype 1g strains). A cluster of subtype 1g is highlighted with a vertical bar. The numbers (>70%) associated with tree branches are indicative of the percentage of 1,000 bootstrap replicates that support the existence of the branches. Bar, 0.01 or 0.05 nucleotide substitutions per site. The full-length genomic sequence of the HC21-0545 strain has been deposited in DDBJ/EMBL/GenBank under accession no. LC650200.**

UK, Spain, and Canada, with a high bootstrap value of 100% (Fig. 3b). Of note, naturally occurring resistance-associated substitutions (RASs) were found in nonstructural (NS)3 (Table 2) and NS5A (Table 3) of the HC21-0545 strain and compared with nine reported subtype 1g strains whose entire coding region sequence has been determined. The HC21-0545 strain possessed three RASs (T54S, S122R, and I170V) in NS3 (Table 2) and six RASs (K24R, M28 L, Q30R/K, H58P, E62Q, and Y93F) in NS5A (Table 3), nearly all of which were commonly found in the reported 1g strains.

Table 2. NS3 RASs in Subtype 1g HCV Strains, Including the HC21-0545 Strain Obtained in the Present Study.

RAS position[a]	HCV-1g strains (Accession no.)[b]									
	AM910652	KJ439770	MN164869	MN782311	MN977327	MW689978	MW689984	MW690007	MW690012	HC21-0545
V36	-[c]	-	-	M	M	-	-	-	M	-
Q41	-	-	-	-	-	-	-	-	-	-
T54	S	S	S	S	S	S	S	S	S	S
V55	-	-	-	-	-	-	-	-	-	-
Y56	-	-	-	-	-	-	-	-	-	-
Q80	-	-	-	-	-	-	-	-	-	-
S122	R	R	R	R	R	R	R	R	R	R
S138	-	-	-	-	-	-	-	-	-	-
R155	-	-	-	-	-	-	-	-	-	-
A156	-	-	-	-	-	-	-	-	-	-
V158	-	-	-	-	-	-	-	-	-	-
A166	-	-	-	-	-	-	-	-	-	-
D168	-	-	-	V	V	E	-	-	-	-
I170	V	V	V	V	V	V	V	V	V	V
L175	-	-	-	-	-	-	-	-	-	-

[a]Wild-type amino acid at and its position related to RAS are indicated.

[b]See Fig. 3 for country in which it was isolated.

[c]Identical to wild-type amino acid.

RAS: resistance-associated substitution

Table 3. NS5A RASs in Subtype 1g HCV Strains Including the HC21-0545 Strain Obtained in the Present Study.

RAS position[a]	HCV-1g strains (Accession no.)[b]									
	AM910652	KJ439770	MN164869	MN782311	MN977327	MW689978	MW689984	MW690007	MW690012	HC21-0545
K24	S	R	R	R	R	R	R	R	R	R
M28	L	L	L	L	L	L	L	L	L	L
Q30	R	-[c]	-	-	-	R	-	-	-	-/R/K
L31	-	-	-	F	F	-	-	-	-	-
P32	-	-	-	-	-	-	-	-	-	-
S38	-	-	-	-	-	-	-	-	-	-
H58	P	P	P	P	P	P	P	P	P	P
E62	Q	Q	Q	Q	Q	Q	Q	Q	Q	Q
A92	-	-	-	-	-	-	-	-	-	-
Y93	F	F	F	F	F	S	F	F	F	F

[a]Wild-type amino acid at and its position related to RAS are indicated.

[b]See Fig. 3 for the country where it was isolated.

[c]Identical to wild-type amino acid.

RAS: resistance-associated substitution

Discussion

In the present study, we experienced the first case of a Japanese patient with HCV subtype 1g, who had a history of receiving plasma exchange therapy in Egypt and who was successfully treated with GLE/PIB. We initially diagnosed him with HCV G4 infection based on the commercial analysis of a short 5'UTR sequence and epidemiological reports showing that approximately 90% of HCV patients in Egypt were infected with HCV G4 (13, 14). However, while we were attempting to determine the subtype within G4, we noticed that the HCV subtype of our patient was 1g based on the analysis of a longer 5'UTR-core region sequence, and subsequently confirmed by the entire genomic sequence analysis. We also found three and six naturally occurring RASs in the NS3 and NS5A regions, respectively, nearly all of which were shared by the reported 1g strains. Despite the presence of such RASs, we successfully treated our patient with a pan-genotypic therapy with GLE/PIB, which is a combination regimen with NS3/4 protease and NS5A inhibitors.

HCV subtype 1g is a so-called 'unusual subtype' and is less prevalent in developed countries than in developing countries. A study conducted at nine French tertiary hospitals showed that only three patients (0.51%) were assigned to G1 non-1a/1b among 584 HCV patients (18). A global epidemiological study that investigated 12,615 patients from

28 different countries across five geographic regions showed that only two patients (0.02%) had HCV subtype 1g; however, many of those countries included in the study were high income and upper to middle income countries (19). Another report from a hospital in the United Kingdom that examined 2,211 HCV patients, indicated that only five patients (0.22%) were infected with HCV subtype 1g; the origin of these cases was Africa (20). Given these previous studies, we emphasize that, the present case is the first case of HCV subtype 1g infection to be reported, with data on DAA therapy and the determination of the full-length genomic sequence.

Currently approved DAA therapies have achieved sustained virologic response (SVR) rates exceeding 95%. However, this novel efficacy of DAA has been demonstrated for HCV patients in upper to middle income countries, where HCV subtypes of 1a, 1b, 2a, 2b, 3a, and 4a prevail (12). In contrast, data on HCV G5, G6, and so-called 'unusual subtypes', including subtype 1g, are scarce, as they are less prevalent in upper to middle income countries (20). A study reported by Childs et al. (20) investigated 63 patients who originated from Africa and who underwent DAA treatments, documenting an SVR rate of 89%. They also reported that the SVR rate decreased to 60% (9/15) in patients with distinct G1 subtypes treated with the NS5A/NS5B regimen (20). Another report examined HCV patients living in the United Kingdom with origins in Africa, who were treated with the NS5A/NS5B regimen, and demonstrated an overall SVR rate of 83% (119/144) and rates of 0% (0/7) and 44% (4/9) in patients with HCV subtypes 1l and 4r, respectively (21). According to a prospective, single-arm trial with ledipasvir-sofosbuvir that was conducted in Rwanda (located in sub-Saharan Africa), the SVR rates were 87% in overall patients with HCV G4 and 56% in those with HCV subtype 4r (22). One reason for the reduced therapeutic efficacy is that the HCV of these unusual subtypes had some natural polymorphisms with resistance to NS5A inhibitors (12). Based on prior studies reporting naturally occurring RASs (23, 24), the full-genome analysis of the present strain (HC21-0545) showed three and six RASs in the NS3 (Table 2) and NS5A (Table 3) regions, respectively, although data of *in vitro* fold resistance levels in subtype 1g replicon are unavailable for these RASs. According to the European Association for the Study of the Liver (EASL) practice guidelines, 12-week sofosbuvir/velpatasvir/voxilaprevir therapy was recommended for the present case with genotype 1 g harboring several NS5A RASs (12). Because sofosbuvir/velpatasvir/voxilaprevir is not available in Japan, Japanese physicians have to use GLE/PIB or ledipasvir-sofosbuvir regimen for HCV patients with 'unusual subtypes'. Moreover, a few data regarding the efficacy of DAAs for patients with HCV subtype 1g have previously been reported; only five patients with HCV subtype 1g were treated with ledipasvir-sofosbuvir (n=3), paritaprevir/ritonavir/ombitasvir dasabuvir (n=1), and grazoprevir/elbasvir (n=1), resulting in the achievement of an SVR in all five patients (20). While there have been no reports concerning the efficacy and safety of DAA for HCV genotype 1g, the GLE/PIB regimen may be suitable because the efficacy of the NS5B-based regimen was suboptimal for patients with 'unusual subtypes', as we mentioned above. Further studies with a greater focus on HCV subtype 1g are therefore warranted.

We initially diagnosed the present patient with HCV G4 based on the results of a commercial analysis. Only a short HCV 5'-UTR sequence was used to construct the phylogenetic tree in the commercial analysis, which may have been sufficient to determine the genotype in Japan, as the prevalent HCV genotypes are limited to subtypes 1b (accounting for 70%), 2a (20%), and 2b (10%). However, it is desirable to determine the genotype using a portion of both the well-conserved 5'UTR-core region and another genomic region, including the NS5B region (25), especially in patients who originate from foreign countries or who are infected abroad, as in the present case.

In this connection, the HCV grouping (26), which is covered by Japanese insurance and commonly used to determine the HCV genotype in daily clinical practice, was assigned to 1 in the present study. In general, in Japanese patients, HCV grouping 1 is thought to correspond to HCV genotype 1b. Therefore, in order to avoid unexpected virological failure, careful interpretation is required for patients who are suspected to potentially have 'unusual' HCV subtypes.

In conclusion, we experienced a Japanese patient who was infected with HCV subtype 1g in Egypt and who was successfully treated with GLE/PIB. A pan-genotypic NS3/4 protease and NS5A inhibitor regimen will be recommended for patients infected with 'unusual' HCV subtypes.

The authors state that they have no Conflict of Interest (COI).

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