Table 4. Effect of B-RTO on laboratory data

	Day 0	Day 1	Day 7
T-Bil (mg/dL)	1.29 ± 0.55	2.21 ± 0.93[b]	1.17 ± 0.46[c]
I-Bil (mg/dL)	0.75 ± 0.30	1.32 ± 0.66[b]	0.66 ± 0.23[c]
Alb (g/dL)	3.40 ± 0.66	Not determined	3.56 ± 0.52[c]
AST (IU/L)	56.2 ± 33.0	87.8 ± 49.6[a]	67.3 ± 51.9[c]
ALT (IU/L)	41.0 ± 31.7	48.9 ± 41.4[c]	53.3 ± 45.0[c]
LDH (IU/L)	383.3 ± 109.4	1066.0 ± 424.7[b]	508.9 ± 105.9[c]
ChE (IU/L)	2084.3 ± 849.3	2422.6 ± 794.5[c]	2225.7 ± 845.1[c]
BUN (mg/dL)	16.2 ± 7.4	17.5 ± 7.5[c]	14.1 ± 5.3[c]
Cre (mg/dL)	0.74 ± 0.19	0.80 ± 0.23[c]	0.65 ± 0.15[c]
PT (%)	67.5 ± 14.1	66.4 ± 12.4[c]	72.8 ± 11.2[c]
Plt ($\times 10^4/\mu L$)	6.94 ± 2.71	6.45 ± 2.35[c]	8.07 ± 3.31[c]
NH_3 (μg/dL)	75.7 ± 37.7	76.6 ± 28.5[c]	63.0 ± 27.0[c]

[a] $p < 0.05$ versus day 0
[b] $p < 0.01$ versus day 0
[c] Not significant
Alb, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, serum urea nitrogen; ChE, choline esterase; Cre, serum creatinine; I-Bil, indirect bilirubin; LDH, lactate dehydrogenase; NH_3, blood ammonia; Plt, platelet count; PT, prothrombin activity; T-Bil bilirubin

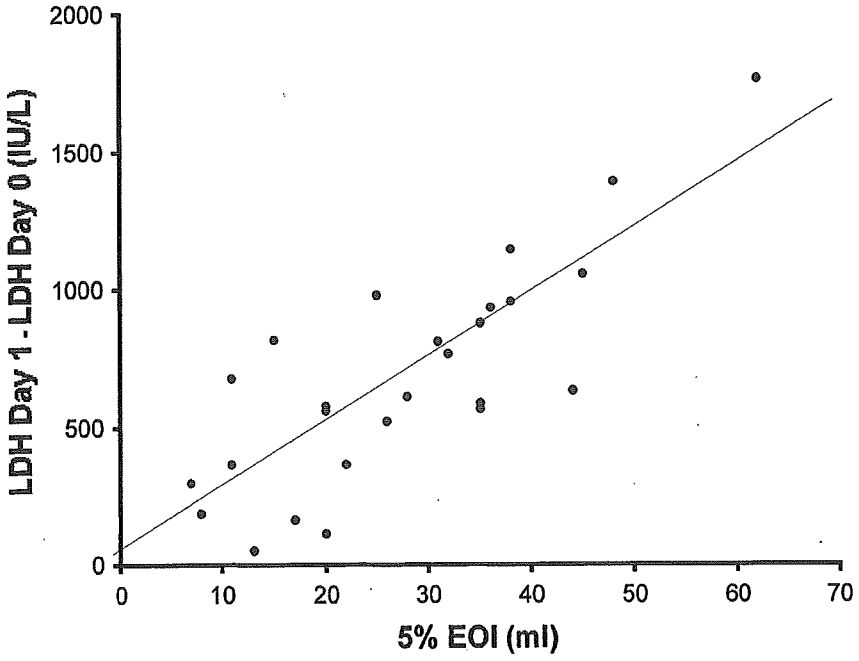

Fig. 5. Correlation between increased LDH ($LDH_{day\ 1}$–$LDH_{day\ 0}$) in the serum and the amount of 5% EOI infused through the gastrorenal shunt or gastrocaval shunt ($n = 26$, $r = 0.81$, $p < 0.001$).

confirmed by CT. Fortunately, the infarct seen in the present study was small and located in the lung periphery, and the ventilatory impairment in this patient was reversible. Arterial partial pressure of oxygen recovered within 7 days to 78.5 mmHg, suggesting that, in addition to pulmonary infarction, some other mechanisms could be involved in ventilatory impairment. For instance, ethanolamine oleate might have impaired pulmonary gas exchange, possibly by alveolar wall edema and lung congestion [19], which was detected by our routine CT. Thus, the influence of B-RTO on ventilatory function needs further investigation including a proper assessment of the incidence of pleural effusion. Routine check of blood gas analysis and chest roentgenogram is recommended in all patients on the day after B-RTO.

Complications that occurred during phase 4, such as PHG and ascites, may be implicated in the increase in portal pressure. Previous studies have shown that obliteration and eradication of esophageal varices by endoscopic sclerotherapy can result in the development or worsening of the mosaic-like pattern of portal hypertensive gastric mucosa [20–23]. As demonstrated by one patient who developed hemorrhagic PHG, obliteration-induced PHG is one of the undesirable outcomes of B-RTO. Bleeding from PHG is likely to be resistant to conservative therapy and may require subsequent endoscopic therapy or TIPS. The effects of B-RTO on PHG should be determined in future studies.

The incidence of gastric ulcers on treated gastric varices was estimated at 9% of B-RTO procedures (Table 3). These

ulcers were small and round and surrounded by the mosaic-like mucosal changes and red marks. Endoscopically they resembled the lesions of PHG, although they were localized on the obliterated gastric varices and immediately surrounding mucosa. These "localized PHGs" and ulcers with unique appearance were likely due to obliteration of both gastric varices and their out-flow collaterals modifying the mucosal perfusion and causing congestion of regional mucosa. Features of localized PHG had disappeared before endoscopy at 8 weeks, indicating improvement of mucosal perfusion within several weeks, possibly by the development of novel collaterals to release the localized congestion, although the exact mechanism is unknown at present. Localized PHG was observed in all patients in whom fundic varices were subsequently eradicated. Thus, absence of this lesion might be considered a marker of unsuccessful treatment. Based on our experience, we recommend periodic follow-up endoscopy, especially at approximately day 7.

One group recently reported amelioration of ascites in two patients after B-RTO, possibly due to improvement of hepatic function reserve and hypoalbuminemia [24]. Similarly, in our study, the rate of ascites retention was only 7%. Only one patient had to stay longer in hospital due to ascites. Thus, despite obliteration of the major part of the portosystemic shunt, the incidence or severity of ascites after B-RTO was not high. B-RTO can improve hepatic encephalopathy through increasing portal blood flow [11, 13]. In the present series, one patient developed a transient grade II hepatic encephalopathy on the day after B-RTO, although this occurred because of high-grade fever and subsequent dehydration. Thus, the development of encephalopathy on the day after B-RTO could have been avoided by sufficient hydration.

Our results showed that increased LDH correlated with the amount of infused 5% EOI. Ethanolamine oleate may increase LDH by inducing intravascular hemolysis [17]. B-RTO resulted in worsening of T-Bil, I-Bil, and AST, which was associated with hemolysis. Renal function was not affected by the B-RTO procedure in our study. However, a close assessment of renal function is important because ethanolamine oleate causes a transient decrease in renal arterial blood flow, hemolytic nephropathy, and tubular necrosis [17], and because deterioration of renal function is frequently seen in cirrhotic patients [25].

In summary, we demonstrated in the present study that the major complications of B-RTO included transient increases in arterial blood pressure, hemoglobinuria, and fever. Further, small pulmonary infarction, pleural effusion, ascites, gastric ulcers with unique appearance and location, and severe PHG were noted in a minority of patients. Most of these complications were mild in nature and reversible. All data indicating deterioration on day 1 was reversed within 7 days. We confirmed the safety and efficacy of B-RTO in this series. If this rate and mildness of complications are confirmed in further series of patients with different etiologies and severities, this technique may become the standard treatment for fundic varices.

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CASE REPORT

Different outcomes of nosocomial infection with hepatitis C virus from the same origin

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Abstract

The outcome of infection with hepatitis C virus (HCV) varies substantially from self-limiting infection to chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma among the individuals. The mechanisms that determine the clearance or the persistence of HCV have not yet been clarified. Here, we experienced two cases of hospital-related infection with HCV from the same origin but with quite different outcomes. One case resolved after an episode of acute hepatitis, while the other case developed a chronic hepatitis although they were infected with HCV of the same origin. Although infected with the virus of the same origin, the clinical and virological courses were completely different. This suggests that host factors play a major role in conditioning the outcome of acute HCV infection.

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Key words: Nosocomial infection; Hepatitis C virus; HLA

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INTRODUCTION

The outcome of infection with hepatitis C virus (HCV) varies from self-remission, chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma[1-3]. About 20% of the people infected with HCV spontaneously clear the virus[4]. On the other hand, the rest of the patients cannot clear the virus and suffer from chronic infection[4]. The mechanisms that determine the clearance or the persistence of HCV have not yet been elucidated. Viral factors such as genotype could be involved in the outcome of the infection[5]. However, what determines the outcome of HCV infection is not totally clear. Here, we experienced two cases of hospital-related infection with HCV from the same origin but with two different outcomes. One case resolved subsequent to an acute hepatitis and the other case became a chronic hepatitis although they were infected with the same viral origin according to viral sequencing. This implies that host factors play a major role in conditioning the outcome of acute HCV infection.

CASE REPORT

A 32-year-old woman (patient 1) and a 71-year-old man (patient 2) were admitted to the same floor of Gunma University Hospital on December 2001. Clinical, biochemical, and serologic profile of patients 1 and 2 are shown in Figure 1.

Patient 1 was diagnosed with idiopathic interstitial pneumonia on February 2001 and followed up as an out patient. She was complicated by a bacterial respiratory infection with dyspnea and she was readmitted on December 21. She showed normal aminotransferase level and was negative for hepatitis B surface antigen (HBsAg) and hepatitis C antibody (HCVAb) on admission. The respiratory infection was treated with antibiotics and the patient gradually improved. Although there were no typical acute hepatitis-like symptoms except for appetite loss, the patient's serum aminotransferase level was elevated during a routine check-up on February 28, 2002. Anti-hepatitis A (HA) IgM antibody, HBsAg and hepatitis B core (HBc) IgM antibody were negative. However, HCVAb became positive at this time. HCV RNA was also positive (850 KIU/mL) and genotype was Ib. Peak level of aspartate aminotransferase (AST) was 1199 IU/L, alanine aminotransferase (ALT) was 1348 IU/L on March 25, respectively. Aminotransferase level became normal on April 15 and continued at a normal level. HCV RNA became negative on April 6 and continued to be negative. She was diagnosed with acute hepatitis C and finally recovered.

Patient 2 was first diagnosed with diabetes mellitus at the age of 44. He was treated with insulin and subsequently admitted for the control of blood sugar on December

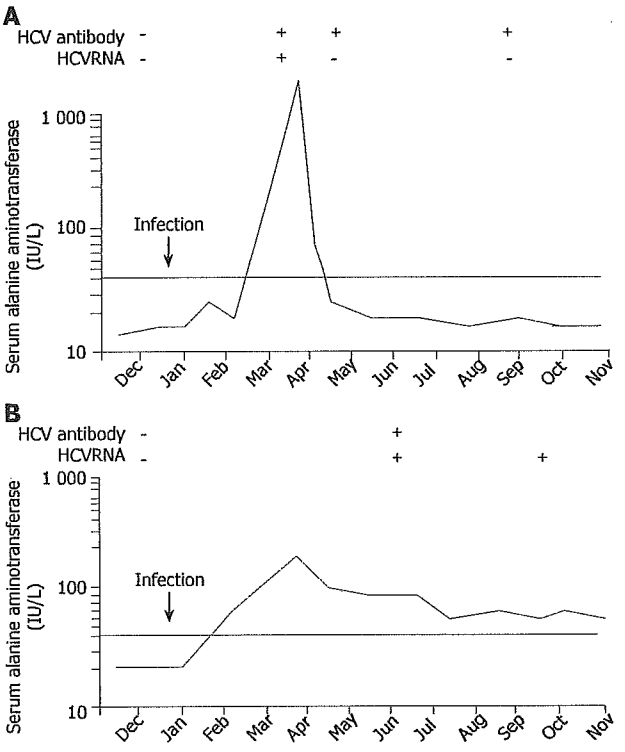

Figure 1 Clinical, biochemical, and serologic profile of patients. **A:** patient 1; **B:** patient 2. HCV antibodies were detected by third-generation tests and HCV RNA was detected in serum by reverse-transcription PCR. Alanine aminotransferase values are shown on a logarithmic scale, and the horizontal lines indicate the upper limit of the normal range.

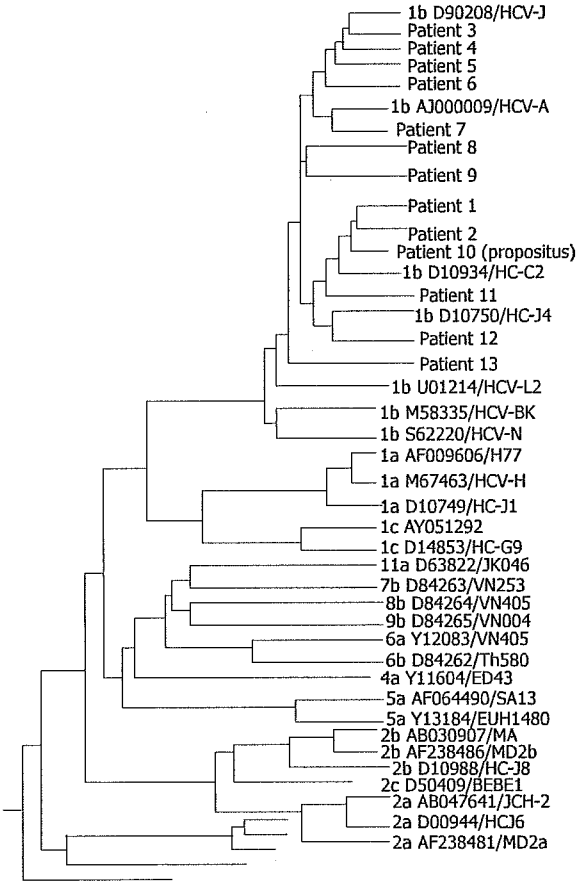

Figure 2 Phylogenetic tree analysis comparing coding sequences in the HCV regions for the envelope glycoproteins E1. For phylogenetic tree analysis, 13 sequences obtained from the 13 patients involved in this study were compared with 33 sequences taken as unrelated controls (genotype and GenBank accession numbers are indicated).

18, 2001. At the age of 69, he was diagnosed with myelodysplastic syndrome. Upon admission aminotransferase levels were normal, and both HBsAg and HCVAb were negative. He was discharged on January 8, 2002 and followed up with his primary physician. He subsequently developed elevated aminotransferase levels and became positive for HCVAb in June 2002. There were no typical acute hepatitis-like symptoms during the follow-up period with his primary physician. Retrospectively, the aminotransferase level of the patient was elevated during a routine check-up in January 31, 2002. HCV RNA was also positive (250 KIU/mL) and genotype was Ib. Peak level of AST was 102 IU /L, ALT was 168 IU /L on March 28. Aminotransferase levels continued to be abnormal for 3 years after the onset. He was diagnosed with chronic hepatitis C.

We believe that HCV infection of both patients occurred during December 2001 to January 2002. There was no suspicious event in the history of the patient suggesting infection such as intravenous drug abuse, blood transfusion, tattoo nor transmission by sexual contact in both cases. Nosocomial infection was suspected and surveyed. HCV genotyping and the nucleotide sequence analysis of coding region for the envelope glycoprotein E1 were performed for the two patients. For the nucleotide sequence analysis, after reverse transcription, the first round of polymerase chain reaction used primers EF1 (sense: 5'-CGCCGACCTCATGGGGTA-3', nt 721 to 739) and ER1 (antisense: 5'-CGACCAGTTCATCATCATATCCCA-3', nt 1 289 to 1 313), and the second-round primers EF2 (sense: 5'-TTGCCCGGTTGCTCTTTTTCTATC-3', nt 837 to 860) and ER2 (antisense: 5'-GCGGTGACCTGATACATGGC-3', nt 1 264 to 1 283). We performed direct-sequence analysis of nested polymerase chain reaction products of 447 bp (nt 837 to 1 283) encompassing the HCV envelope glycoprotein E1. The polymerase chain reaction products were gel purified and sequenced by automated sequencer. The HCV genotype of both patients was Ib. The sequences of HCV E1 region from both the patients were 99.7% in agreement. We considered that the origins of both infections were the same and these two hepatitis infections were hospital related. We checked up on all the patients who were admitted to the same floor from December 18, 2001 to January 8, 2002, the suspicious infection period in question. There were 16 patients positive for HCV antibody. These 16 patients were examined for the genotype of HCV and 11 of them were Ib. The nucleotide sequences of E1 region in these 11 patients (numbered patient 3-13) were compared by the same method. Phylogenetic tree analysis comparing coding sequences in the HCV E1 region are shown in Figure 2. For phylogenetic tree analysis, 13 sequences obtained from the 13 patients involved in this study were compared with 33 sequences taken as unrelated controls. One patient had close nucleotide sequenc-

ing with patients 1 and 2. A 70-year-old man (patient 10, named as propositus) with liver cirrhosis was considered as the propositus of this hospital-related infection of HCV. He was admitted for treatment of hepatic encephalopathy from December 26-29.

Thus, patient 1 had a complete resolution of acute hepatitis C, while patient 2 developed a chronic hepatitis C infection although both were infected by the same HCV strain (propositus, patient 10). Although it was not fully elucidated how the nosocomial infection occurred, intravenous catheter flushing with heparin retrieved from a multidose heparin solution in saline was thought to be one of the causes of the infection.

DISCUSSION

Although the same HCV strain infected two patients, each patient showed a completely different outcome. One case was cured from acute hepatitis and the other case developed chronic hepatitis although they were infected with HCV of the same origin. Primary HCV infection is poorly characterized because most patients are asymptomatic and, therefore, it is rarely diagnosed[3,6,7]. Larghi *et al*[8] reported the outcome of an outbreak of acute hepatitis C supposedly infected from a common source. Among the 14 patients followed up, 8 patients resolved spontaneously and 6 patients developed chronic infection[8]. The incubation period and the outcome of the acute phase of the disease were highly variable. The average incubation period was 10 wk, but the range was from 6 to 28 wk. In our case, the supposed incubation periods of patients 1 and 2 were 9 and 5 wk, respectively.

The clinical and virologic course also varied, both in patients in whom the infection resolved spontaneously and in those developing chronic infection[8]. This suggests that host factors play a major role in conditioning the outcome of acute HCV infection[9,10]. Thus, the host immune system is important for the clearance of virus. In view of the host factors, specific MHC class II alleles were reported to influence susceptibility or resistance to persistent HCV infection[10,11]. The associations of self-limiting HCV infection with HLA-DRB1*1101 and HLA-DQB1*0301 have been independently reported by some groups[10,11]. Persistent HCV infection was associated with HLA-DRB1*0701, and HLA-DRB4*0101. In our case, HLA was not fully evaluated in all the patients. However, propositus had DRB1*0901, DRB1*1502, DQB1*0303, and DQB1*0601. Patient 2 had DRB1*0901, DRB1*1403, DQB1*0303, and DQB1*0301. HLA-DQB1*0301 was not a self-limiting factor in our case.

We were able to determine the propositus of the HCV infection; however, the route of infection was not fully understood. There was no procedure identified in these patients to directly cause the infection, such as endoscopy, surgery or hemodialysis. Finally, flushing of intravenous catheters with heparin retrieved from a multidose heparin solution in saline was thought to have caused the infection. Since January 2002, our department has been using heparin solution packed for individual use for flushing of intravenous catheters. The period of this nosocomial infection was before the use of individual packed heparin solution was instituted. All had long-lasting intravenous catheters. Multidose vials used for flushing or treatment had probably been contaminated during periods of overlapping treatment. Contamination of multidosing vials was the most likely mode of HCV transmission[12]. Therefore, use of such vials should be avoided.

We experienced two cases of hospital-related infection of HCV from the same origin followed by different outcomes. One patient was cured of acute hepatitis and the other case developed chronic hepatitis although both were infected by the same propositus. Although they were infected by the same source, the clinical and virologic course was completely different. This suggests that the host factors play a major role in determining the outcome of acute HCV infection.

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Case report

Adult onset type II citrullinemia as a cause of non-alcoholic steatohepatitis

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Adult onset type II citrullinemia (CTLN2) is an autosomal recessive disease accompanied with hyperammonemia and a sudden onset of psychiatric disorders. We demonstrated three male patients with CTLN2 having a liver histology of non-alcoholic steatohepatitis (NASH). Patients with NASH were analyzed for the causative gene of CTLN2, SLC25A13 and discussed.

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Keywords: **NASH; CTLN2; Citrullin; Pathology; Mutation**

1. Introduction

Non-alcoholic steatohepatitis (NASH) has been increasingly recognized as one of the major types of progressive liver disease. NASH may be the most common liver disease with a high prevalence in obese individuals and those with type 2 diabetes. In addition to these nutritional or metabolic causes of NASH, drugs and genetic disorders have been reported to induce NASH [1–3]. We herein propose adult onset type II citrullinemia (CTLN2) as a new genetic cause of NASH.

CTLN2 is characterized by episodes of neurological symptoms associated with hyperammonemia involving disorientation, abnormal behavior (aggression, irritability and hyperactivity), seizures, coma, and potentially death from brain edema [4]. The causative gene of CTLN2 has been identified to be SLC25A13 which encodes citrin, a Ca-binding mitochondrial aspartate-glutamate transporter [5], and a citrin deficiency causes not only CTLN2 in adults, but also idiopathic neonatal hepatitis with intrahepatic cholestasis (NICCD) in neonates [4,6]. One of the clinical and pathological features of CTLN2 and NICCD is the presence of a fatty liver [4,7]. We herein show hepatic steatosis associated with fibrosis and inflammatory change compatible with NASH. The pathogenesis of NASH was also investigated based on the mutation of SLC25A13.

2. Patients and methods

2.1. CTLN2 patients

Three patients with genetically and enzymatically diagnosed CTLN2 were analyzed for their clinical and histopathological findings according to the Brunt classification [8]. None of the three male patients had a history of habitual alcohol drinking (Table 1).

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Table 1
Clinical and pathological data of three patients with type II citrullienemia

Patient	1	2	3
Age at onset CTLN2	37	16	42
Sex	M	M	M
Wt. (kg)/Ht (cm), BMI (kg/m^2)	41.5/160,16.2	43/162,16.4	53/172,17.9
Clinical course	Found by a psychiatrist to demonstrate somnolence at night with elevated NH3	NICCD at 2 months of age. Vomiting and consciousness disturbancy at 15 y. o. Fulminant hepatic failure	A liver biopsy revealed steatohepatitis because of liver dysfunction. NH3 was high and a psychiatrist observed dys-orientation with triphasic wave in EEG
NH3 (20–50 nm/dl)	350–600	530	716
Citrulline (28–48 nm/ml)	460	814	119.7
Arginine (70–128 nm/ml)	249.3	183.3	154.3
Mutation of SLC25A13 (see text 2.3)	[IV]: S225X&[V]: IVS13+1G>A, compound hetero	[II], IVS11+1G>A, homo	[V], IVS13+1G>A, homo
ASS in liver (2.59±1.13 U/g)	0.032	0.0038	0.55
PSTI (4.2–12 ng/ml)	Not done	43	150
GOT/GPT (IU/l)	24/33	163/101	52/79
alb (g/dl)	3.6	4.1	3.9
Plt (×10,000/mm^3)	13.5	19.7	20.7
t-chol (mg/dl)/TG (mg/dl)	112/103	193/100	175/nd
Liver histology (#1)			
Grade/steatosis (%)	1/30%	3/70%	2/50%
Stage	1	4	2
Periportal/pericentral	mild/mild	severe/mild	moderate/mild
Mallory body	−	+	+
Liporgranuloma	−	+	+
Glycongen nucleus	+	+	+
Treatment	Sodium glutamate, sodium citrate	Liver transplantation from his father	Argimagte, KM (#2), lactulose
Prognoisis	Good	Fair after transplantation	Fair

#1, modified from Ref. [8]; #2, Kanamycin

2.2. NASH patients

Fourteen patients with NASH, 4 men and 10 women ranging from 28 to 70 years of age (mean±SD=55.3±18.6), who showed various degrees of NASH, were analyzed for 14 loci of the causative gene of CTLN2, SLC25A13, by the method described below.

2.3. Detection of citrin gene SLC25A13 mutations

Fourteen in 21 mutation sites of citrin gene SLC25A13 were analyzed by the conventional method, since 94% of CTLN2 patients have been diagnosed at these 14 loci. The 13 known mutations, [I]–[XI], [XIV] and [XX], were detected by PCR-RFLP and/or multiple GeneScan/SNaPshot methods, as described previously [5,6,9,10], and a novel [XIX] mutation will be reported in the near future elsewhere (Tabata et al. in preparation). Genomic DNA samples from the patients were used after obtaining their written informed consent. This study was performed in accordance with the Declaration of Helsinki and its amendments and was approved by the Ethics Committee of the Faculty of Medicine at Gunma University and Kagoshima University.

3. Results

3.1. Clinical profile of CTLN2 patients (Table 1)

Patient 1 had been healthy until developing night somnolence and thus, visited a psychiatrist for the treatment. Hyperammonemia and deregulation of amino acid including citrullinemia [11] were demonstrated. He was diagnosed to have CTLN2 and had an extremely low activity of argininosuccinate synthetase (ASS) of the liver. After the discovery of SLC25A13 and the identification of mutations [5], compound heterozygous mutations were found. Patient 2 was a 16-year-old boy with fulminant hepatic failure who was diagnosed to have CTLN2 based on a genetic analysis [13]. He underwent a partial liver transplantation from his father and had done well for 5 years after the operation [12]. Thereafter, we found that he suffered from neonatal intrahepatic cholestasis related to NICCD symptoms, at 2 months old of age [13]. Patient 3 was suffered from a sudden onset of consciousness disturbance with hyperammonemia. A serum amino acid analysis revealed hypercitrullinemia and he was finally diagnosed as CTLN2 by a genetic analysis.

3.2. Liver histology of the CTLN2 patients

A liver biopsy under the guide of ultrasonography was performed in patients 1 and 3. The liver histology of patient 2 was obtained from the explanted liver at the transplantation (Table 1 and Fig. 1).

Patient 1 showed grade 1 steatosis (Fig. 1(a)) and stage 1 pericentral and periportal fibrosis (Fig. 1(a)). Focal necrosis

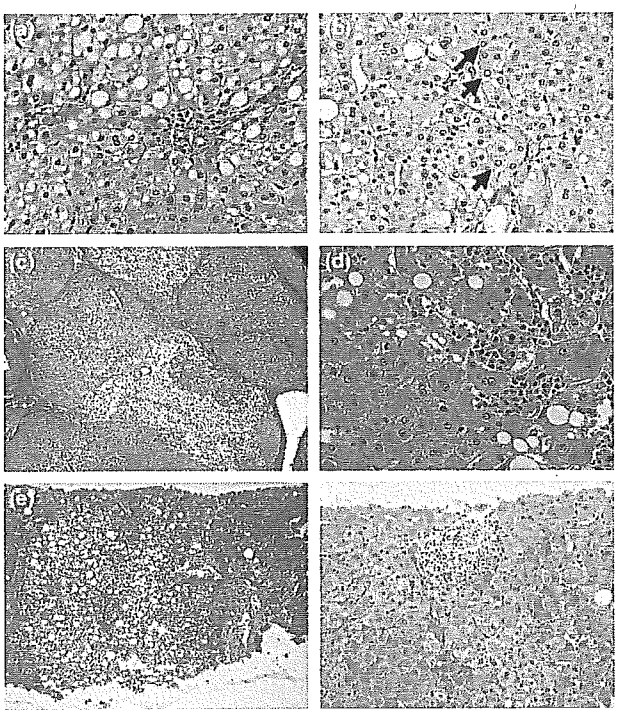

Fig. 1. (a) and (b) Histopathology of patient 1, 37-year-old male. (a) Portal inflammation and periportal fat deposition (HE, 80×, 200×). (b) Glycogen nuclei (arrow), large and small droplets were observed. (c) and (d) Histopathology of patient 2, 16-year-old male. (c) Stage 4 cirrhotic change with pericentral fatty change was observed. Azan Mallory 40×. (d) focal necrosis with neutrophils infiltration. HE 200×. (e) and (f) Histopathology of patient 3, 42-year-old male. (e) Steatosis in zone 2 and 3. Azan Mallory 40×. (f) Granuloma formation was seen. HE, 80×.

with mononuclear cell infiltration (Fig. 1(a)) and lots of glycogen nuclei were found (Fig. 1(b)). Patient 2 had stage 4 fibrosis, namely cirrhosis with pericentral steatosis (Fig. 1(c)) and grade 2 inflammation with neutrophils infiltration (Fig. 1(d)). Mallory body, granuloma formation around central vein and moderate hemosiderosis were noted (not shown). Patient 3 showed pericentral fibrosis accompanied with zone 2–3 steatosis (Fig. 1(e)) and inflammatory change with granuloma formation (Fig. 1(f)).

3.3. Citrin gene analysis in patients with NASH

None of the fourteen NASH patients had a mutation in 14 loci of SLC25A13 gene.

4. Discussion

Due to recent advances in the understanding of NASH, in addition to the acquired causes of NASH such as diabetes mellitus and jejuno-ileal bypass, genetic causes have been reported such as abetalipoproteinemia, galactosemia and so on [1–3]. We herein advocate that CTLN2 is a disease associated with NASH. All three presented cases with CTLN2 demonstrated NASH in different grades of inflammation and stages of fibrosis. Because of the accumulation of NADH in the cytosol due to the dysfunction of citrin, over production of fatty acid and the suppression of the metabolism of fatty acid may simultaneously occur in hepatocytes thereby easily inducing steatosis [4,7]. After the induction of fat deposition, a second hit, which has yet to be clarified, could evoke and inflammatory response, namely NASH.

Previous reports have showed some genetic predisposition of NASH, such as tumor necrosis alpha promoter [14] and a hemochromatosis gene [15] but these changes are only considered to partially contribute to the etiology of the disease. Ordinarily, patients with CTLN2 are lean or not obese regarding their body structure in contrast to most of NASH patients who are tend to be obese. All three patients of CTLN2 patients analyzed in this study had a low body mass index (BMI) under 18 kg/m^2. Five of the 14 patients with NASH were not obese with BMI of under 25, but over 20 kg/m^2. All 14 NASH patients including this five had no detectable known mutations in citrin gene. Although the frequency of NASH by CTLN2 is not supposed to be high, we have heard an episode that one lean patient with a fatty liver who suddenly suffered from a consciousness disturbance and later developed CTLN2 (personal communication).

In conclusion, CTLN2 has thus been histologically proven to be one of the causes of NASH. Although an analysis of the citrin gene in patients with NASH failed to find any mutations, we should therefore include CTLN2 in the differential diagnosis of NASH, especially in lean patients with a fatty liver and mental disturbance.

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総 説

肝細胞癌に対する肝移植
—移植適応の拡大をめざして—

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Liver transplantation for hepatocellular carcinoma —To expand the indication—

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Summary : Liver transplantation has been recognized one of the treatments of choice for hepatocellular carcinoma (HCC) in Japan in the cases compatible with Milan criteria since January 1, 2004. Milan criteria were mostly cited as the guide lines of liver transplantation for HCC and broadly accepted as the ultimate criteria for liver transplantation for HCC because of significantly long tumor free survival. The original data of the Milan criteria were evaluated ten years ago and the revised criteria were proposed from UCSF, Kyoto University and other institutions. They have challenged to expand the indications of liver transplantation for HCC and gained reasonable results. The discrepancy between imaging diagnosis and pathology has been demonstrated, but the inconsistency did not relate to the prognosis, which meant the precise preoperative imaging is applicable enough to assess the prognosis of liver transplantation. On the other hand, some of extra-Milan patients showed fair prognosis. Several of such extra-Milan patients with good prognosis were reported in the 30th Liver Cancer Case Meeting at Tokyo, in November, 2004. The reason of good prognosis of these cases has not been fully clarified, but histological poor differentiation, vascular invasion and increased size of the tumor were indicated as poor prognostic factors. New prognostic markers including messenger-RNA of alpha-fetoprotein in the serum and oncogenes or their receptors expressed in HCC tissue could be predictable for the diagnosis of HCC recurrence in transplanted liver. Further study to establish donor selection especially in cases of living related donor mostly used in Japan and viral eradication would be mandatory in addition to the prediction of the recurrence of HCC.

Key words : hepatocellular carcinoma (HCC), transplantation, criteria, recurrence
〔*Liver Cancer* **11**(1) : 1-8, 2005〕

はじめに

肝臓癌に対する肝移植は2004年1月に保険適応となり，ミラノ基準内(後述)という条件付きでわが国における肝癌治療の選択肢の一つとして認知さ

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Table 1 Indication and results of liver transplantation for HCC

Year	Patients	Criteria	Neoadjuvant therapy	Survival (%)	Mean time (years)	Reference
1996	48	One tumor≦5 cm or≦3 tumors≦3 cm	TACE or PEIT or resection	75	4	Milan[3]
2001	60	One tumor≦6.5 cm or≦3 tumors ≦4.5 cm and total tumor diameter ≦8 cm	TACE or PEIT	75	5	UCSF[4]
2003	56	No size restriction, No macroscopic vascular invasion	TACE or PEIT or RFA or cryoablation or resection	54.6*	3	Kyoto[5]

*: 91% in cases within Milan criteria, TACE : transcatheter arterial chemoembolization
PEIT : percutaneous ethanol injection therapy, RFA : radio frequency ablation

れた。肝不全患者の最後の治療手段であるという本来の肝移植が，肝不全になっていなくても肝癌自体の進行度によっては，むしろ移植によって並存する肝硬変，肝不全を同時に治してしまうという究極の治療法として選択され，欧米をはじめわが国でも症例が増加している。わが国における脳死肝移植は脳死が認められてから7年，第1例目の脳死移植が行われてから5年，2004年12月の段階で24例に行われたにすぎない。そしてその生存率は83%(4名死亡)である。そのため圧倒的に生体肝移植が増加し，なかでも成人例では，肝癌症例に対する移植が肝癌を合併しない肝硬変への移植よりも多いのが現状である[1]。すなわち，治療困難な肝癌症例がわが国の成人肝移植レシピエントの最も多い疾患ということになる。これは同様の傾向が欧米などでも見受けられる[2]。

I. ミラノ基準を見直す—10年の時を経て

ミラノ基準は，「単発であれば5 cm以下，多発であれば3 cm，3個以内の遠隔転移のない肝癌」が肝移植のよい適応であるとする世界のstandardともいうべき基準であるが[3]，その基準を拡大したUCSF基準[4]，京都大学の基準[5]などが新たにミラノ基準を越えた肝癌患者への移植適応の拡大基準として提唱され一定の成績を示している(Table 1)。基準を越えるものに対する移植をして当然の結果ながら再発率は高い。しかし基準内にもかかわらず早期に再発する例も存在する一方で，再発を危惧しつつ，基準を逸脱する進行肝癌に対して生体移植であるという特殊性から移植を行ったにもかかわらず無再発で長期生存している例も報告されている[5-9]。今後は移植治療の長期的予後改善をめざして，肝癌への肝移植の厳密な選択を迫られることになる。ミラノ基準はあくまでもミラノにあるイタリア国立がんセンター消化器外科の移植チームが自分たちの肝移植症例から多変量解析によって導いた彼らの基準である。移植医療に遅れをとったわが国が基準としてそれを取り入れたのはある程度はしかたのないことであるが，本来はわが国独自の基準を設けなければ日本の肝癌患者の置かれた特殊性，すなわち背景がC型，B型の肝硬変であり，肝癌に対する局所療法，手術療法の成績が良好で，脳死移植のドナーがないため移植自体はもっぱら生体肝で行われるなどの点が反映されない可能性がある。

ミラノ基準が論文発表されたのは1996年であるが，対象となった48例の切除不能の小肝癌に対して行われた肝移植は1995年9月までに施行された肝癌患者の成績から導きだされたものである。すなわちデータそのものは10年前のものである。そもそも肝予備能低下や腫瘍の部位が手術などに適してはいない症例で，かつ肝癌自体は非進行例を選んで解析したもので，全体の症例数も多くはないし，大きなものは再発しやすいというそれまでのデータに基づいた解析である。それまでに多くのtrialがなされたにもかかわらず，移植後生存率が向上しなかった時期に，4年生存率75%を達成する基準を提示したことには意義があり(Fig. 1a)，臨床系では最高ランクの*N. Engl. J. Med.*に掲載された点も長く支持された理由の一つであろう。この論文

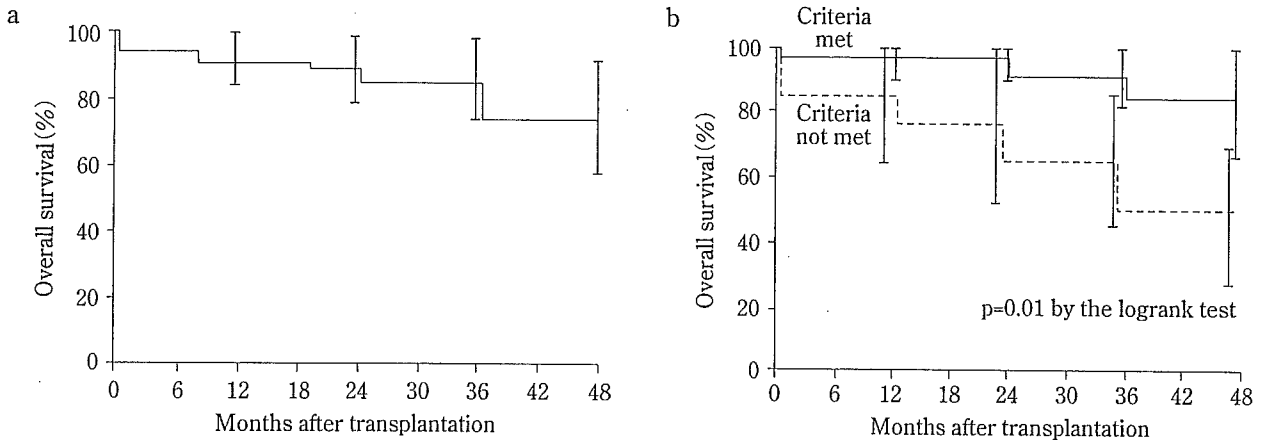

Fig. 1 a : Overall survival after liver transplantation in 48 patients with small hepatocellular carcinoma and cirrhosis.
b : Correlation of post-transplantation pathological confirmation of early-stage hepatocellular carcinoma with overall survival. Modified from reference 3 (Milan criteria, reference 3).

のもう一つのポイントは，摘出肝での病理学的検討では13例(27%)が基準を逸脱していたことを報告している点で，ある意味画像診断の限界を示しているといえる。そもそも全肝検索は従来剖検でしか成し得なかったが，肝移植の普及により患者が生存中に行えるようになり，移植後の予後に摘出全肝検索の結果を反映させることが可能になった。摘出肝の病理的なミラノ基準合致例では4年生存率は85%に達する(Fig. 1b)。ではミラノ基準の患者のprofile，特に画像診断はいかになされたのか。原文には明確にCTAPで行ったと記載されている。すでに10年経過しようとしているこの基準において，移植前検査がCTAPで決定されており，一致率が73%であったという。わが国においては，画像診断は，厳格に血管造影，CTA，CTAPで確認するなどの規定はなく，保険適応上にもその画像診断のやり方まで規定はしていない。診断能の向上がさらに基準を変えていく可能性は十分に考慮すべきである。京都大学の摘出肝の病理組織学的検索からの検討でも68例の肝癌で，移植前の画像による病期診断が，22例(32.3%)において移植後全肝検索と比べ，過小評価したとしている[10]。われわれの検討でも，移植前にはミラノ基準を満たしていた10例中移植後の病理で実に6例(60%)がミラノ基準を逸脱していたが，これらは全例にCTA，CTAPが行われたわけではない。しかし移植前の画像診断がミラノ基準を満たしていれば，たとえ摘出肝の全肝病理検索で基準を逸脱しても，移植後1年で再発は1例にすぎず，大きな再発のリスクにはなっていない[11]。第40回日本肝癌研究会ワークショップの総まとめをした市田らの報告でも，画像とexplantでの腫瘍個数の合致率は37%にすぎない[7]。脳死移植に関してはしばらくはミラノ基準を踏襲していく方向と思うが，単発の最大径や腫瘍数の拡大などの付加的なevidenceが追加され，特に生体肝移植の場合どこまで適応が広げられていくのかは今後の課題である。保険適応を考慮して4個ある腫瘍のうち1個を切除ないしはablationして3個にし，基準内と考えて移植をするという考えについては否定的な考えが多く，あくまでもできてしまった腫瘍を治療していない段階で評価してのミラノ基準であることを銘記すべきである。6 cmの腫瘍をTAEで縮小させ，摘出肝臓では5 cmとなっていた肝癌症例に移植し，早期に肝臓と肺に転移を生じた報告なども参考になろう[12]。

II. 移植後再発

マウントサイナイ病院における肝癌311例への移植のまとめによれば，57例(18.3%)が中央値約1年で再発し，最も多い再発部位はグラフト肝そのもの(47%)，肺(44%)，骨(33%)である[13]。再発腫瘍に対しても肝切除，肺切除，RFA，副腎切除などが

なされ，移植前の生検部位への胸壁転移切除まで報告されている。そして移植肝への再発に対してさらに肝切除をすることが，予後を改善することを報告している[13]。京都大学の生体からの肝癌への移植56例のまとめで再発部位としては肺(3例)，副腎，横隔膜，後腹膜(各2例)が多く，移植肝での再発は1例のみであったという[5]。日本全体のまとめでは，原発性肝癌316例に対する生体肝移植で，40人(13%)が再発を来し，これら再発患者自体の再発時期としては3, 6, 12, 24, 36か月でそれぞれ10, 43, 75, 93, 100%の再発率であった。1年以内に3/4が再発し，なかには2年以降に再発する患者もみられるという。再発部位としては6例(15%)が肝，肺が8例(20%)，骨9例(22.5%)で，複数の部位に再発する例が17例(42.5%)と最も多かった[14]。

III. 移植後再発予測

日本では症例数の最も多い京都大学の報告では移植後再発に寄与する有意な因子としては組織型(高・中分化型＜低分化型)と脈管侵襲が抽出され，ミラノ基準そのもの，腫瘍最大径，腫瘍個数，移植前後の化学療法の有無，腫瘍マーカーなどは有意な差はなかったとしている[5]。Todoらの日本全体の肝移植研究会のまとめでは，多変量解析で門脈浸潤，AFP，腫瘍径，腫瘍分布(片葉，両葉)が有意であり，組織学的分化度も相関が高度であるとしている[14]。Klintmalmらは，多施設410例の肝癌への移植例において，移植後再発を来すものでは腫瘍径5 cm超，脈管侵襲の他に組織学的分化度の低さをあげている[15]。このように対象群，症例数によって若干の違いはあるが，一般的に進行すればするほど再発が多くなるということであり，組織学的分化度は総じて再発の指標として取り上げられている。では移植には肝生検での組織学的確認が必須であろうか。移植待機中のpoor risk患者に対して，複数個ある肝臓癌を皆針生検し，すべての分化度を的確に，副作用や癌細胞散布[16]などなしに診断できるとは到底思われない。移植自体が8割医療(2割は周術期に失われる)という現況で，肝癌に対する移植が5年生存率，10年生存率を何割めざすのかによって適応基準も当然変化してくる。肝移植ではないが，第13回肝癌症例検討会(1996年)では肝癌の「早期再発例」が主題として取り上げられ，根治したと考えられたにもかかわらず早期再発した症例が報告されており(*Liver Cancer* 第2巻第2号，1996)，その原因も組織学的に低分化，悪性度の高さ，門脈浸潤，腫瘍の流出静脈の存在などがあげられているが，それから10年近く経過した現在でもこれらの詳細なメカニズムが明確にされたとはいい難い。

再発防止のための処置として，移植前のTAEの評価は未だ定まっていない。総じて腫瘍径の大きいものでは腫瘍を壊死，縮小することで無再発生存率が有意に上昇することが報告されている[17,18]。一方，カテーテルによる治療で肝動脈が損傷を受ける可能性も懸念されるが，おおむね直接移植に影響するほどの血管損傷は来さないとされている。いずれにしても移植を第一に考えて肝癌を治療するという肝癌治療のアルゴリズムが確立していない現在，肝癌に対する治療を加えないで移植を待つわけにはいかず，何らかの治療を加えざるを得ないとすれば，それらの治療の移植に対するbenefitを十分考慮して，治療法を選択していくことになろう。

日本全体のまとめでは，ミラノ基準適合例では106例中3例のみの再発であったにもかかわらず，逸脱例119例では22例(18.5%)が再発を来し，累積3年再発率は35%であるとしている[14]。これはミラノ基準の優秀性を再確認したには違いないが，逸脱例の65%は無再発であることのほうがはるかに興味深い。これらの無再発例の検討を是非詳細に追加報告して欲しいものである。

肝癌の遠隔転移の確定にFDG-PETを用いる施設が増加している。確かにガリウムシンチグラフィに比べ感度がよく，骨シンチグラフィに比べてもより正確に骨転移を描出できることからも現時点では広くscreeningする意味では有用と思われるが[19]，肝細胞の糖代謝系酵素の発現から，高分化型では正常細胞との違いが少なく，判別が困難であるとされている。中～低分化型肝癌の感度は高いことから，遠隔転移の拾い上げの有用性はあり得るが，原発巣自体の診断上の感度はCT 90%に比べ，FDG-PET 55%とされており，false negativeも常に念頭に置かなければならない[19]。

Table 2 Cancer related genes for the prediction of HCC recurrence after transplantation (modified from Marsh JW, et al : reference 22)

Gene	Full name of gene	Function
APC	Adenomatous polyposis coli	regulates transmission of the contact inhibition signal
CDKN2A	Cyclin-dependent kinase inhibitor 2A	induces cell cycle arrest
MET	Met proto oncogene	MET-HGF/SF spnaling affects cell proliferation, cellular shaping and motility
MYC	Avian myelocytomatosis viral Oncogene Homolog	activates transcription; may regress gene expression
DCC	Deleted in colorectal carcinoma	features in common with cell-adhesion molecules; may participate in cell-cell and cell-matrix interactions
OGG1	8-oxoguanine DNA glycosilate	repairs DNA damage causes by exposure to reactive oxygen induces entry into mitosis
p34	Cyclin-dependent kinase	induces entry into mitosis
TP53	Tumor protein 53	activates the expression of adjacent genes that inhibit growth and/or invasion
PTEN	Phosphatase and tensin homolog	blocks cell cycle progression in the G1 phase

IV. 細胞学的/分子生物学的再発予測

これらの移植基準を画像診断ですべてを決しようとする方法には限界があり，病理学的分化度はあくまで摘出肝臓で正確に判定できるのであって，いずれの方法にも限界があるとすれば，当然細胞学的/分子生物学的な方法で予測の可能性を探ることになる。末梢血中のAFP-mRNAをPCRで測定し，微量な循環血中の癌細胞を同定し，それによって移植後再発を予測し得るとする報告がある[20,21]。20個の肝癌があるにもかかわらず，AFP-mRNA陰性の肝癌症例で無再発3年生存例を経験していると報告している[21]。しかしこれも，AFP非産生肝癌であればfalse negativeを生じる恐れがあり，さらなる検討が必要であろう。最新の生物学的進行度[22]を示した報告によれば(Table 2)に示す9の腫瘍関連遺伝子のloss of heterozygosityを活用すれば再発を100%予測し得たという。すなわち部分的アレルの欠失が3未満の患者では100%無再発であったという。さらに3以上の患者は高率に再発し，5年生存率は1割程度であったとしている。

V. ミラノ基準逸脱無再発例

ではミラノ逸脱例にもかからず無再発である例の特徴は，いかなるものであろうか。本検討会(第30回肝癌症例検討会)の主題演題「興味ある転帰を来した肝癌に対する肝移植症例」の一つとして報告された京都大学の1例は門脈腫瘍栓陽性のT4N0M0, Stage IVA, 22歳，女性例で，化学療法でAFPが5,789 ng/mlから239 ng/mlに減少した症例であるが，父親からの右葉グラフト移植により5年無再発生存中であるという[6]。また東京医科大学の1例もvp3, 最大径5 cmの中分化型肝癌で，移植後化学療法を併用し2年無再発であるという[8]。群馬大学の症例は転移性肝癌としては唯一移植適応ありとされるカルチノイドの肝転移例であるが，原発巣，リンパ節転移まで切除し，転移巣である肝臓を移植し，2年無再発であるという[9]。こういう例をみると，術前，術後の化学療法による腫瘍の減少，さらに肝癌自体の生物学的悪性度が最も移植後再発に関与する因子ではないかとの印象を受ける。さらに症例の積み重ねが必要であるが，そのためにもミラノ基準逸脱例の成績良好例を丹念に解析する必要と，それ以前に逸脱例の移植を，特に生体の場合，肝外転移なしを最低条件として増やして検討する必要があると考える。

再発の予測をするためには本来論外なことであるが，画像診断の精度の向上，統一が求められる。不正確な画像診断では当然進行度の正確な評価が適さず，また画像診断から移植までの時間がたちす

ぎれば当然進行するわけで，ミラノ基準に合致していたのは3か月前だというのでは，explantの評価が移植前の画像と異なるといっても，時間がたって進行したためとなれば当然起こり得ることである。画像の種類にしても，移植症例は最低限CTA，CTAPで評価することを義務付けてもよいのではないかと考えるが，しかし移植直前には血管造影すら負担になって施行しかねる患者も多い。

VI. ドナー

肝癌への移植に限定される話題ではないが，ドナーの問題にも触れておきたい。「肝癌への生体移植」と「脳死からの肝癌以外の肝不全に対する移植」について，レシピエントを同じ基準で選択してよいのか，社会的共有とされる脳死ドナーと生体ドナーではおのずと適応選択の自由度に差があってもよいと思われるし，レシピエント・ドナーの年齢制限をつけてよいのか，などの議論がある。ドナーの高齢化は明らかにレシピエントの生存率を低下させる[23]。肝癌の場合，基準を越えた再発の可能性が高いレシピエントに対して，高齢ドナーや脂肪肝グラフトを適応するというmarginal donorという表現がある[24]。HCV陽性患者でも同様に陰性者に比較し長期生存は得にくいわけでmarginal donorを活用すべきであるとの主張もある[23]。外科医が移植の成績を向上させたいという意向を当然ながら示すのと裏腹に，肝臓内科の現場では，とにかく臨死状態の肝不全，肝癌患者を生還させたいという患者，家族の要望に応えたいという葛藤がある。これはしばらくは生体移植の直面する正解のない問いとして留めておきたい。

一方，わが国でも2003年に生体肝移植ドナーの第1例目の死亡例を経験し，生体ドナーのその後を追跡する必要性が高まり，肝移植研究会が全国調査を実施した[25]。そのまとめをいえば，おおむね術後経過は良好であるが，順調に，完全に手術前の状態に回復したと回答したのは5〜6割であり，半数は何らかの後遺症を訴えていたというものである。肝移植のドナーの手術も，特に右葉の場合など，かなりの大手術となる。群馬大学でも2004年より内科でドナー外来を開始した。そこでの実感は内科医からみれば，ドナーは手術痕のケロイドなども含めれば100%が身体的合併症を有しているといわざるを得ない。さらに健常な成人がさらされる，移植による仕事上，経済的さらには社会的な制約を思えば，部分肝切除による生体肝移植は至上の奉仕，献身ともいうべき行為といえよう。決して生体肝移植を否定するものではなく，ドナーには大小の合併症が必ず発症すると，むしろ率直に情報開示すべきで，それを理解し，乗り越えた上でのドナー志願であり，やり終えた後の達成感，家族愛の確認，賞賛などが十分代償してあまりあるものとなり得ると考える。反面，移植が不成功に終わった場合の生き残ったドナーの不満，心理的な非到達感については公にされることは少ない。生体ドナーに対する医療保障制度はなく，健康な社会人がある日から病人として職場などでも差別を受けることがないようにする制度の確立など未解決な問題は多い。

ま と め

肝癌に対する肝移植が医療として成立している大前提には，初期肝癌は転移が少ないという特性がある。現状では肝不全がなく，肝癌自体に対する治療が可能な場合はそれが最優先されるが，癌自体の治療が困難となり移植が考慮される場合は当然ながら進行癌が含まれてくる。最大限のミラノ基準3 cm，3個以内の肝癌が両葉にわたって存在すれば，脈管侵襲がないという前提ですでにStageⅢであり，日本肝癌研究会の報告では5年生存率はoverallで41.8%と移植の成績を下回る[26]。肝移植が重度の肝不全患者も含めて行われていることを考慮すれば，当分の間はStageⅢの肝癌に対する選択肢として肝移植を念頭に置かねばなるまい。脳死移植に多くを望めないわが国で生体肝移植がどこまで発展し，わが国独自の基準と例外的な症例を特例として見いだせるようになるのか今後の症例の積み重ねと検討が必要である。内科医の立場からすれば，生体移植であればこそミラノ基準に固執することなく，混合診療の導入も見据えた自由診療下での，ドナーと患者の要望に応える形での例外的な移植も当分は行われなければ上記の結論はでないと考える。この再発率ひいては生存率が，どの程度であれば許される数字かは施設によって異なっており，よりよい成績をめざすにはむしろriskyな症例

には挑まないということになる。統一した基準を設け，基準外の症例にどこまで挑戦するのかは施設によって異なってよい状態なのか，あるいは規定すべきかについては今のところ正解はない。ある施設では移植不能といわれ，他の施設で移植を受けた症例もあるように聞く。長期生存をめざすというより，目前の死を回避するための移植が許されるか否かは，混合診療が導入されれば当然対応が変わってよいと思われるし，その施設，医師がどこまで患者，家族の要望に応える姿勢を示すか否かの選択にかかっている。移植後早期の合併症による死亡を減らすのと同等に免疫抑制下における肝炎ウイルス再発の克服，そして肝癌再発の予防，再発癌の治療など，肝臓内科，肝臓移植外科の連携がますます重要になっていくものと考える。

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総 説

RFA後に急速に増悪した肝細胞癌の検討

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Aggressive recurrence after radiofrequency ablation (RFA) of hepatocellular carcinoma

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Summary : Radiofrequency ablation (RFA) is a novel technique for the treatment of hepatocellular carcinoma (HCC) and has become more prevalent because of its feasibility, effectiveness and safety. However, a fatal tumor progression after RFA has been reported in the literatures. In this review article, 10 cases of rapid HCC progression after RFA therapy were reviewed out of 6 reports. According to the analysis of the 10 cases, possible risk factors for rapid HCC progression after RFA were the use of umbrella-type needle and the location of HCC near the major portal branch. The characteristics of the rapid HCC progression itself after RFA were the portal tumor thrombosis, multiple or massive recurrence in the same segment or lobe and poor differentiation of recurrent HCC. The mechanism of rapid tumor progression after RFA remains unclear and further studies are necessary to evaluate the incidence and pathogenesis of this underestimated complication.

Key words : hepatocellular carcinoma (HCC), radiofrequency ablation (RFA), aggressive recurrence

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はじめに

ラジオ波焼灼療法(RFA)は内科的な肝腫瘍の局所治療法として1996年, Rossi ら[1]により報告された。以降わが国でも施行可能となり, 当初は保険適応外であったが2004年4月より保険適応となり肝細胞癌(HCC)の局所治療法として急速に広まっている[2,3]。通常RFAは1回の焼灼で直径約3 cm, 最近の機種ではさらに広い範囲の病変を完全壊死させることが可能であり合併症の頻度も低く, その有効性と安全性が確立されつつある。まだ長期の予後はでていないが5年までの生存率は, 究極の局所療法である肝切除術に近い治療成績が報告されている[4]。そういう背景のなかで, 2001年に Seki らにより RFA 後急速に HCC が進行した症例が報告され[5], 合併症として RFA 後短い期間において HCC が急速に増大する症例のあることがクローズアップされ, その続報が続いた。しかし, 現時点において“RFA後に急速に増悪したHCC”と一概に表記してもその定義が不明確である。また腫瘍治療後の再発あるいは進展・転移を考慮する上で,

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HCCの場合は多中心性発癌の可能性を完全に除外できないのが実態である。そこで本稿ではRFA治療直後に画像診断にてHCCが完全に治療されているにもかかわらず，治療後4か月以内に治療部位の周辺を含めHCCが肝内に急速に増大・発生した，あるいはRFA治療時に認められなかった門脈腫瘍栓が認められたものと定義し，過去に報告された文献を基にその病態を検討する。また，今回の検討ではいわゆるneedle tract tumor seedingは検討の対象外とした。

I. 発生頻度

文献的に検索し得たRFA後に急速に増悪したHCCの症例はSekiらのcase reportの後に5報告，計13例[6-10]報告されている。そのうち本稿の定義に合致する症例は，Sekiらの1例を加え10例である。その頻度にまで言及しているものとしては，Nicolaらの0.68%(1/148)とRuzzenenteらの4.5%(4/87)がありその頻度に若干の開きはあるが，当科においてもそのような症例は108例中1例(0.93%)認められている。したがって“RFA後に急速に増悪したHCC”の発生頻度は数%程度と考えられ，当初危惧されたほど高頻度な合併症ではないようであるが，一般に副作用，予期せぬ転帰などは報告されない頻度が高く，この数字以上である可能性も考えられる。

II. 報告例のまとめとその特徴

そこで今回検索し得た上記の10例を論文に記載のある範囲でTable 1のごとくその特徴をまとめてみた。症例は58～75歳までの男性7名，女性3名である。背景肝はHBV，HCVあるいはアルコールに伴う慢性肝疾患のあるHCC患者である。臨床病期やHCC stageは論文の記載では不明な症例が多かった。治療対象になったHCCの平均径は34 mm(20～45 mm)であった。10例の特徴としては，①“umbrella type”である展開針式のRFA針(RITA, Le Veen)の症例が80%(8/10症例)と1本針であるCool-tip typeの使用頻度に比べその比率が高い，②治療前のHCCの存在部位は門脈や肝静脈の血管系に近い症例の比率が高い，③再発のHCCの腫瘍進展は画像上，門脈浸潤を認めているものが記載のある範囲では71%(5/7症例)と高頻度に認められた，④再発はほぼ全例でRFAした肝の同一区域内(あるいは片葉)の肝臓に多発あるいは境界不明瞭にび漫性に認められている，⑤治療前のHCC組織診の言及はないものの，急速に増悪したHCCの腫瘍組織診は80%(4/5症例)が低分化型のHCC，残りの1例が中分化型のHCCであったという5項目であった。また，これらの症例はいずれも治療後急速に肝不全などに陥っており，予後は非常に悪く，RFA治療後1か月から8か月(中央値3か月)で死亡していることも特徴的であった。

III. 発症機序に関する考察

次にその発生機序につき，Table 1の10例のデータおよび過去の報告者らの考察を交えて検討した。まず，その機序を推測する上で前出の①～④と⑤を二つのグループにして分けて考察したい。

1. 肝内への腫瘍細胞の播種

まず前者である①～④について，つまり①使用されたRFA針はumbrella typeが多く，②HCCはRFA前には血管の近傍に位置している比率が高く，③，④その再発形式もその病変の門脈の支配領域を含む形で門脈浸潤や肝内多発転移を起こしている点である。HCCの腫瘍細胞がどのように門脈を含む広範囲な肝内に播種したかに関しては，RFAの治療過程によりその腫瘍細胞が門脈系を介し肝臓内に播種した，という考えが大多数である。われわれも同様に推察している。日常のRFA治療時に腹部超音波画像上，治療部位よりバブルが脈管系に流れるのを頻繁に経験する。同様に治療中に腫瘍細胞が門脈に流れ込み，その門脈の支配領域の肝臓に広がるという考え方である。その予想される機序は次のとおりである。RFAの治療熱によりHCCの腫瘍内圧が上昇する。そしてその上昇した腫瘍内圧により，あるいはumbrella typeのRFA針により腫瘍と門脈に交通が形成されることにより，HCCの腫瘍細胞がまず門脈に流れ込む。その後，その門脈を経由して腫瘍細胞が肝内に播種していくというものである。この推測を裏付けるように，Nicoliらは RFA治療後の患者に血管造影を行い，21例中3例(14.3%)に血管造影にて確認できる程度のarteriovenous fistulaを確認しており，その3