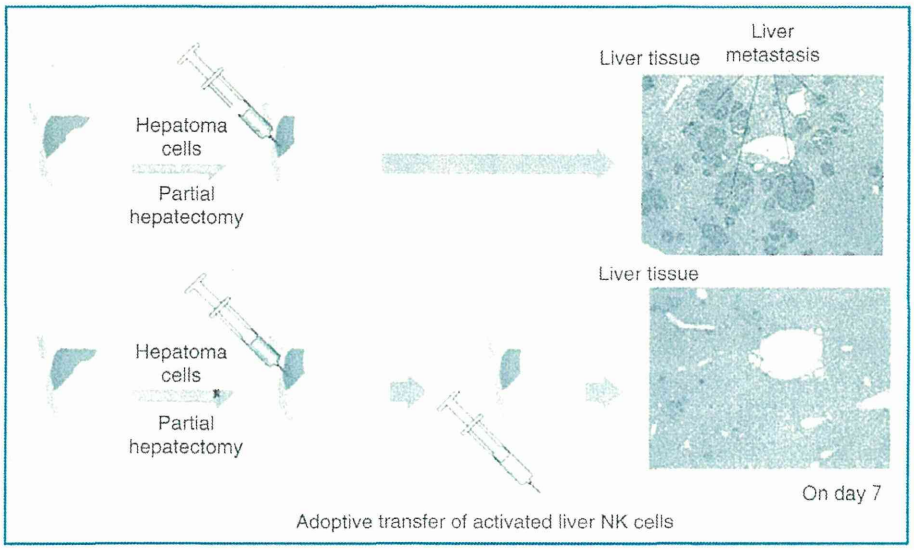

図5　TRAIL 表出肝 NK 細胞の移入によって肝癌増勢を抑制できる（マウスモデル）

B6 マウスの肝臓を 70 %切除し Hepa1-6 ヘパトーマ株を門脈内移入すると，肝内に肝癌の転移巣を確認できる（1 週間後）。しかし，TRAIL を表出した同系の肝 NK 細胞を静脈内移入すると（ヘパトーマ移入 3 日後），肝癌の転移巣は消失する。

（文献 13 より引用）

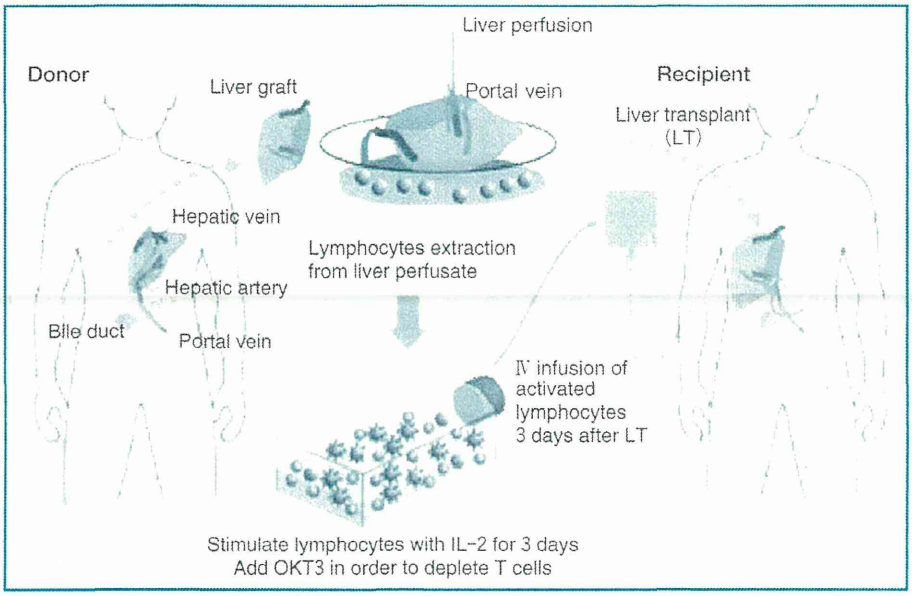

図6　癌再発防止を目的とした肝臓癌合併肝移植におけるドナー肝臓内 NK 細胞を用いた術後補助免疫療法の臨床応用（広島大学倫理委員会　通知番号 414 号）

肝移植の際に，ドナー肝臓灌流排液から抽出した NK/NKT 細胞を IL-2/抗 CD3 抗体刺激で IFN-γ 産生能を誘導した後に，肝癌患者あるいは HCV 性肝硬変患者に対する肝移植後に移入する。

（文献 18 より引用）

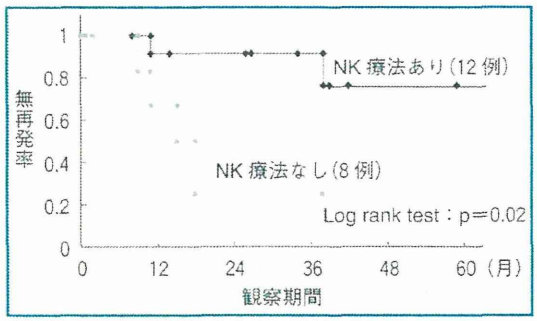

図 7　ミラノ基準外症例では，NK 療法施行群においてHCC 再発率が有意に低下した

後の検討課題も多く残されている。術前の血小板減少症と脾腫の程度が術後の血小板減少の予測因子となるため，肝移植後早期に IFN 療法を開始する場合には，移植時に脾摘を施行する場合もある[17]。

最近われわれは，前述の肝由来リンパ球移入療法を施行した HCV 肝炎感染症例では，肝移植後に血中 HCV ウイルス量が有意に減少することを確認した(図 8)[18]。HCV 感染ヒト肝細胞キメラマウスへのヒト肝由来活性化リンパ球を移入した実験でもこの現象は再現可能であった(図 9)。重度免疫不全マウスと u-PA transgenic マウス(肝臓特異的に u-PA 遺伝子を発現し肝障害を生じる)を掛け合わせた u-PA/SCID マウスに，ヒトの肝細胞を経脾的に移植すると，90 %以上ヒト肝細胞に置換される。ヒト肝細胞キメラマウスに HCV RNA 高値患者(genotype Ib)の血清を移入すると，ヒト肝細胞における HCV の感染と複製が確認できる。HCV RNA 患者血清移入 2 週間後に肝由来活性化リンパ球を移入すると，HCV 感染は回避された。しかし，抗 HCV 中和抗体によってこの効果は消失し，肝由来の NK 細胞から産生される IFN-γ が，HCV の複製を抑制したためと考えられた。

一般に，ウイルスが感染すると NK 細胞の非特異的応答によりウイルスは排除される。しかし，HCV 感染では HCV の E2 蛋白と NK 細胞上の CD81 分子の結合によって NK 細胞機能が抑制され，高頻度に持続感染に移行する。肝由来の NK

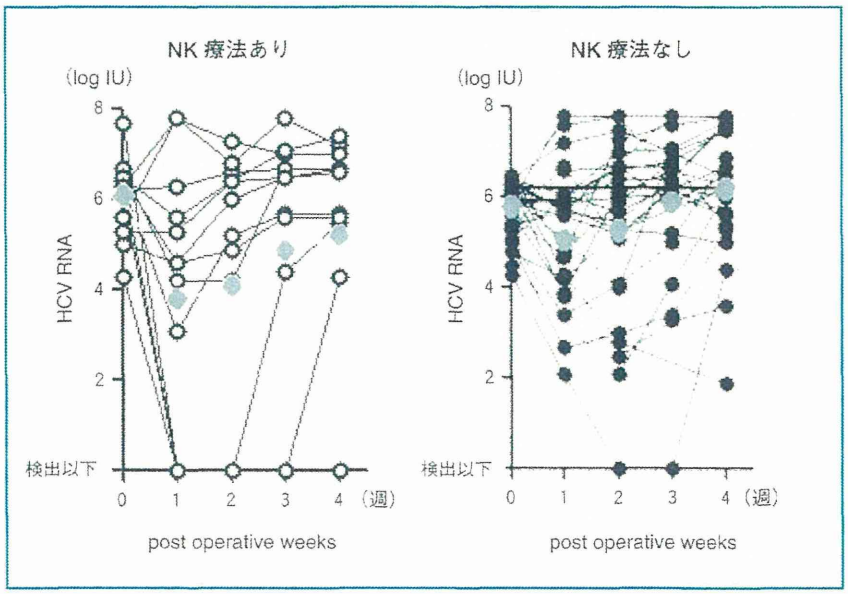

図 8　NK 細胞移入療法後には，血清中 HCV RNA 量が低下する

n＝13 each group．グレーの丸は平均値。

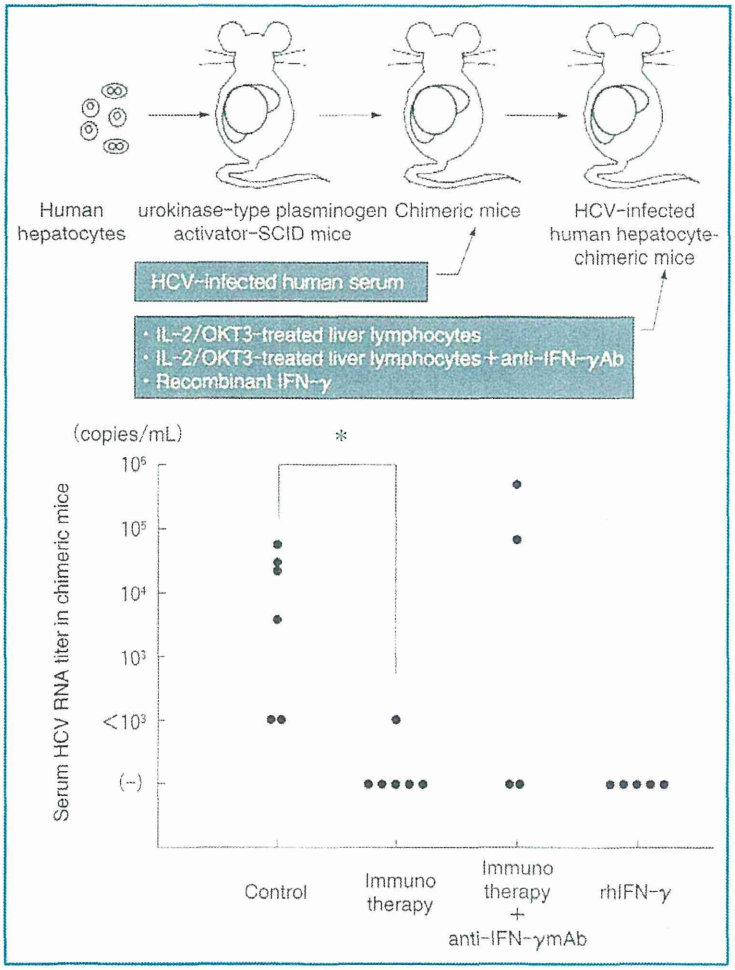

図9　HCV感染ヒト肝細胞キメラマウスへのヒト肝由来活性化リンパ球移入実験

重度免疫不全マウスとu-PA transgenicマウス(肝臓特異的にu-PA遺伝子を発現し肝障害を生じる)を掛け合わせたu-PA/SCIDマウスに，ヒトの肝細胞を経脾的に移植すると，90％以上ヒト肝細胞に置換される．ヒト肝細胞キメラマウスにHCV RNA高値患者(genotype Ib)の血清を移入すると，ヒト肝細胞におけるHCVの感染と複製が確認できる．HCV RNA患者血清移入2週間後に，肝由来活性化リンパ球(±抗IFN-γ中和抗体)あるいはリコンビナントIFN-γを移入した．　(文献18より引用)

細胞をIL-2/抗CD3抗体存在下で培養した場合，CD81を介した抑制機構に抵抗性を示し，IFN-γを介した強いHCV複製抑制効果を誘導しえることが確認された(特開2007-332103)[17]．しかし，術後1度きりのNK細胞移入では，一過性に血中HCV DNA量が低下するもののウイルスの排除には至ることはない．必要な時期に十分量のNK細胞を移入することができれば，既存あるいは新規の抗ウイルス療法との併用により，HCV肝炎を根治できる可能性がある．そこで，末梢血リンパ球，骨髄造血幹細胞あるいはiPS細胞から，IFN-γ産生能の高いNK細胞を分化誘導するリモデリング法の確立を目指して基礎的研究を継続している．末梢血リンパ球を用いる研究では，至適濃度のIL-2/抗CD3抗体の存在下で4週間培養すると，$CD3^-CD56^+$ NK細胞と$CD3^+CD56^+$ NKT細胞が3,000倍以上に増殖し，80％の純度で回収可能で，IFN-γ依存性抗HCV効果を誘導することが可能である[19]．今後，臨床応用の可能性を検討したい．

5．肝由来NK細胞移入療法の重傷細菌感染予防効果

肝由来NK細胞移入療法は現在まで1年以上の観察期間を終えた経験症例は28例であるが，1年生存率は100％である．NK細胞療法により，細菌血流感染/菌血症の発症率が有意に低下したことが反映された結果と解釈している[20]．移植後の免疫抑制剤使用下では，獲得免疫応答は著明に抑制され，周術期の感染防御には自然免疫応答へ比重がかかる．今後，NK細胞療法を細菌感染予防目的の適応へ拡大することを考慮している．

まとめ

肝臓外科領域、特に肝臓移植後の周術管理において、免疫学的防御器官として肝臓がおす機能を掌握し、戦略的に制御する可能性について、LSEC、NK細胞、NKT細胞を対象としたわれわれの研究を紹介した。

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Original Article

Surgical treatment for portosystemic encephalopathy in patients with liver cirrhosis: Occlusion of portosystemic shunt in combination with splenectomy

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Aim: Operative ligation of the portosystemic shunt may control hepatic encephalopathy effectively, but the subsequent increase in portal vein pressure (PVP) leads to high mortality. Splenectomy can decrease inflow into the portal system, resulting in decreased portal pressure.

Methods: We retrospectively examined the effect of splenectomy in combination with shunt closure on portosystemic encephalopathy.

Results: Clinical symptoms of encephalopathy disappeared in all six patients who underwent splenectomy in combination with portosystemic shunt ligation, with the exception of one patient who had relapsing encephalopathy after 6 months. Follow-up computed tomography showed complete obliteration of the portosystemic shunts, except in the one patient with relapsing encephalopathy who underwent balloon-occluded retrograde transvenous obliteration for the remaining splenorenal shunt 8 months after surgery. PVP significantly decreased after splenectomy. PVP did not increase to the baseline PVP value after ligation of the shunts, except in two patients who had elevated PVP after surgery: PVP increased from 18 to 19 mmHg after ligation in one patient and from 18 to 23 mmHg in one patient.

Conclusion: Splenectomy followed by surgical ligation of the portosystemic shunt may be feasible and safe for cirrhotic patients with portosystemic shunts.

Key words: hepatic encephalopathy, portosystemic shunt, splenectomy, surgical ligation

INTRODUCTION

IT IS KNOWN that there are two types of encephalopathy related to liver cirrhosis: portosystemic encephalopathy and end-stage hepatic encephalopathy in severe liver dysfunction. The portosystemic shunt involves blood flow from mainly the supramesenteric vein to the systemic vein, and results in high systemic blood ammonia levels. For hepatic encephalopathy caused by a portosystemic shunt, surgical or interventional radiological closure of the shunt has been reported. Interventional radiology (IVR) represented by balloon-occluded retrograde transvenous obliteration (B-RTO) has been developed as a new therapy for portosystemic encephalopathy.[1–3] Improvement of liver function due to increased portal venous blood flow after B-RTO for gastric varices has been reported.[4,5] However, B-RTO is not expected to provide long-term effects for portosystemic encephalopathy, and it is not necessarily indicated for portosystemic encephalopathy.[6–9] Radiological occlusion of portosystemic shunts is frequently accompanied by ascites or bleeding from collateral vessels due to increased portal vein pressure (PVP).[1]

Operative ligation of the shunt may control encephalopathy effectively, but the formation and rupture of esophageal varices that develop due to the subsequent increase in PVP are associated with high mortality.[10] Simple ligation of the shunt alone is not adopted presently in clinical settings. Splenectomy has been performed as a part of Hassab's operation, or esophageal

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transection, to control variceal hemorrhage.[11] Moreover, splenectomy results in decreased portal pressure[12,13] and reversal of hypersplenism,[14] and it has been concurrently performed for patients with small-for-size (SFS) liver grafts in the setting of living-donor liver transplantation (LDLT).[15–17] Therefore, splenectomy in combination with closure of the shunt may efficiently obliterate the portosystemic shunt without increasing PVP.

The aim of the current study is to investigate the feasibility and safety of splenectomy in combination with closure of the shunt for portosystemic encephalopathy in patients with liver cirrhosis.

METHODS

Patients

BETWEEN JANUARY 2003 and September 2011, 60 patients with portal hypertension related to liver disease underwent splenectomy at Hiroshima University Hospital. Among them, six patients underwent splenectomy in combination with closure of portosystemic shunts for hepatic encephalopathy. Table 1 lists the clinical characteristics of the patients. The median age was 62 years (range, 55–73). The cause of liver disease was chronic hepatitis C virus infection in four patients, alcohol abuse in one patient and chronic hepatitis B virus infection in one patient. The Child–Pugh score was 8 in two patients, 9 in three patients and 10 in one patient. Esophageal varices, which were found in four patients, were classified as F2 in one patient and F1 in three patients according to the endoscopic criteria of the Japan Society for Portal Hypertension.[18] According to the classification of consciousness disorders of the Japan Society for Portal Hypertension,[19] four patients had episodes of grade IV encephalopathy (coma), and two of six patients had shown grade II encephalopathy for the last 12 months. In all cases, large portosystemic shunts were confirmed by dynamic computed tomography (CT). One patient had a large left gastric azygos vein and para-umbilical vein shunts, and five patients had large splenic renal shunts. All patients had large spleens. The indications for surgery were as follows: IVR had been performed without success in three cases, and shunt occlusion by IVR was considered difficult in three cases because of huge vessels.

Surgical procedure

Six patients underwent splenectomy followed by closure of portosystemic shunts. During surgery, a midline incision or inverted "L" incision was used, and

Table 1 Patients' characteristics and results

Patient no.	Age	Sex	Etiology	Child–Pugh score	Liver biopsy	Portosystemic shunt	Follow up (months)	Recurrence of encephalopathy	Status	Comment
1	62	F	HCV	8	F3	Splenorenal	36	–	Alive and well	
2	63	M	HCV	8	F4	Splenorenal	30	–	Alive and well	Tx of HCC
3	73	M	HCV	9	F4	Splenorenal	23	–	Alive and well	
4	55	M	Alcohol	10	F4	Splenorenal	22	6 months	Alive and well	B-RTO after surgery
5	62	F	HBV	9	F3	Splenorenal	19	–	Alive and well	
6	62	F	HCV	9	F4	Left gastric azygos and para-umbilical vein	6	–	Alive and well	

B-RTO, balloon-occluded retrograde transvenous obliteration; F3, chronic hepatitis; F4, cirrhosis, HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; Tx, treatment.

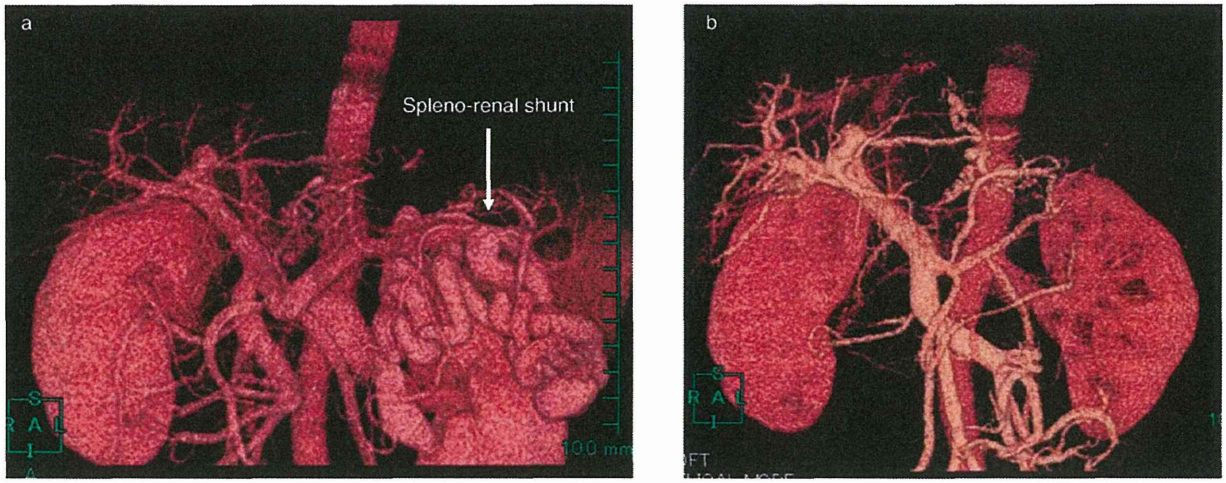

Figure 1 Three-dimensional computed tomography (CT) of the portal vein in case 1. (a) CT before surgery showing huge splenorenal shunts. (b) CT after surgery showing disappearance of a splenorenal shunt.

an antithrombotic catheter was inserted via the jejunal vein immediately after laparotomy. The top of the catheter was positioned in the portal vein. A transducer was used to measure the PVP during surgery, and the catheter was removed before the abdominal operative wound was closed. Splenectomy was performed with ligation and division of the vessels at the splenic hilum. Clamp tests were performed on portosystemic shunts before ligation of the shunts, and portosystemic shunts were ligated if PVP was less than the PVP measured immediately after laparotomy (baseline PVP) or if there was a less than 50% increase in the baseline PVP measured at the clamping test of shunt vessels. Liver biopsy was performed before the abdomen was closed. For follow up, CT was performed preoperatively and at 1 week and 1 and 6 months after surgery, or when indicated clinically. Serum ammonia levels were measured monthly.

Statistical analysis

Student's paired *t*-test was used for comparison of perioperative laboratory data. *P*-values less than 0.05 were considered significant. Statistical analyses were performed using SPSS ver. 16.0 software (SPSS, Chicago, IL, USA).

RESULTS

CLINICAL SYMPTOMS OF encephalopathy disappeared in all six patients within 5 days after surgery. Furthermore, all patients were free from encephalopathy during the median follow up of 23 months (range, 6–36), with the exception of one patient (case 4) who had relapsing encephalopathy and re-elevation of the serum ammonia level after surgery. He underwent B-RTO for the remaining splenorenal shunt, and was alive without encephalopathy at the time of writing this manuscript. The follow-up CT showed complete obliteration of the portosystemic shunts in all patients except the single patient (case 4) who had relapsing encephalopathy (Fig. 1). PVP significantly decreased after splenectomy in all six cases (Fig. 2). Although PVP increased after ligation of the shunts, it increased to the baseline PVP or less in cases 1, 3, 5 and 6 and was only 1 mmHg higher than the baseline PVP in case 2. In case 4, the baseline PVP was 18 mmHg; PVP decreased to

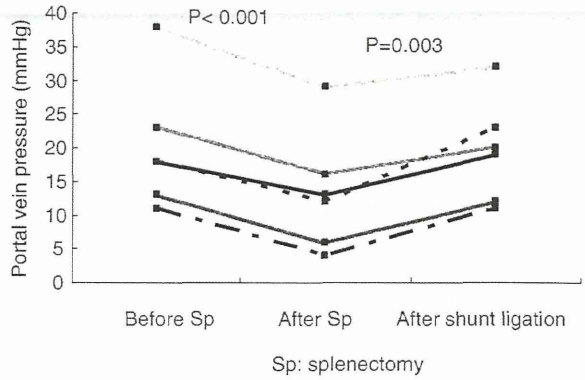

Figure 2 Changes in portal vein pressure during surgery.

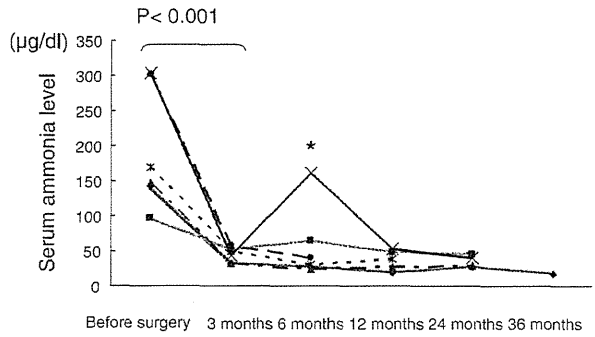

Figure 3 Changes in the serum ammonia level. *One patient (case 4) with relapsing encephalopathy underwent balloon-occluded retrograde transvenous obliteration for the remaining splenorenal shunt 8 months after surgery.

12 mmHg after splenectomy but increased to 29 mmHg at the clamping test of all splenorenal shunts. Thus, several peripheral splenorenal vessels were ligated, and the PVP measured before closing the abdomen eventually increased to 23 mmHg (Fig. 2). The maximum serum ammonia level significantly decreased 3 months after surgery compared with the level before the surgery (Fig. 3). The diameter of the portal vein trunk significantly increased at 1 month after surgery (Fig. 4). Hematological tests conducted before and 3 months after the operation revealed a significant increase in platelet count, from 7.1 ± 0.7 to $20.5 \pm 2.1 \times 10^3/\mu L$ ($P < 0.001$). Examination of liver biopsy specimens showed that four patients had liver cirrhosis and two patients had chronic hepatitis

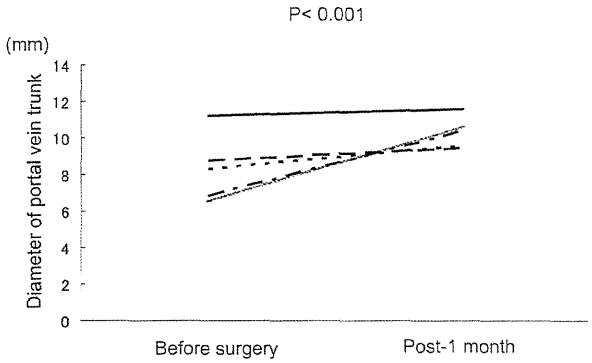

Figure 4 Changes in the diameter of the portal vein trunk before and after surgery. One patient (case 6) with large left gastric azygos vein and para-umbilical vein shunts has been excluded, because the portal flow of the left portal vein decreased due to ligation of the para-umbilical vein.

(Table 1). With regard to the operative characteristics of six patients, the mean operative time was 273 min (range, 180–284), and the mean operative blood loss was 450 mL (range, 180–920). Five patients did not receive operative or perioperative transfusion, whereas one patient received operative transfusion including 4 units of red cell concentrate and 10 units of fresh frozen plasma because of preoperative anemia (hemoglobin level, 7.6 g/dL) and operative blood loss (920 mL with ascites).

Major complications such as development/enlargement of esophagogastric varices were not seen after surgery. However, minor postoperative complications associated with surgery developed in all six patients: three patients developed transient ascites, which was controlled by diuretics medications, and four patients developed splenic vein thrombosis, which was treated by the administration of antithrombin III and warfarin.

DISCUSSION

CHRONIC RECURRENT HEPATIC encephalopathy is often associated with portosystemic shunts in patients with cirrhosis. Encephalopathy of this type is usually treated with lactulose and an oral branched-chain amino acid supplement. In general, IVR including B-RTO may effectively treat portosystemic encephalopathy that is intractable to pharmacotherapy. However, the IVR procedure and the preventive effects of IVR are occasionally limited in a population of patients with portosystemic shunt, because it is not technically feasible to insert numerous coils safely into huge portosystemic shunts.[3] The occlusion of a huge para-umbilical vein shunt is considered difficult by IVR.[8] Percutaneous transhepatic obliteration has the risk of migration of sclerosing agents to the systemic circulation. Several studies have reported poor long-term effects of IVR for portosystemic encephalopathy. Kato *et al.* reported that encephalopathy relapsed in four of six patients who underwent B-RTO for portosystemic encephalopathy between 6 and 30 months after the procedure.[7] Zidi *et al.* showed that long-term improvement was obtained in only one of seven patients who underwent shunt embolization.[6]

Shunt embolization by IVR as well as surgical ligation leads to the subsequent increase in PVP, which may worsen esophageal gastric varices and result in the formation of new portosystemic shunts.[20] Sakurabayashi *et al.* showed that the PVP of two patients with complete shunt occlusion significantly increased from 110 to

220 mmH_2O after shunt embolization.[3] Meanwhile, Yoshida *et al.* presented the benefits of portosystemic shunt obliteration followed by partial splenic embolization (PSE).[21,22] In these studies, PVP tended to increase without significance after obliteration of shunts combined with PSE by IVR, while PVP significantly increased after obliteration of shunts without PSE by IVR.[21] They concluded that PSE can reduce the PVP to a level similar to the PVP before the obliteration of portosystemic shunts and that a new portosystemic shunt is unlikely to develop at lower PVP.

Splenectomy can decrease inflow into the portal system, resulting in a decreased portal pressure.[12,13] In the current study, the PVP decreased after splenectomy, which is consistent with the findings of previous reports. In LDLT settings, the problems of SFS syndrome have become evident, an increased rate of graft loss.[23,24] Although the pathogenesis of SFS graft syndrome seems to be multifocal, an increased sinusoidal pressure in a graft is thought to be the major determining factor. Shimada *et al.* showed that splenectomy decreased portal pressure and improved the outcome of LDLT.[12] Although the mechanism by which splenectomy improves the liver function is unclear, the improved liver function might be associated with a decrease in the PVP after splenectomy. On the other hand, splenectomy may cause the decrease in portal vein flow and rather leads to liver dysfunction. In the current study, portal flow had been partially stolen via the large portosystemic shunts before ligation of the shunts. However, after ligating the portosystemic shunts, the portal flow to the liver increased, as shown in Figure 4, which showed that the diameter of the portal vein trunk increased as measured by CT.

In the current study, splenectomy followed by closure of the portosystemic shunt did not result in an elevation in PVP after portosystemic shunt ligation in all but two patients. Futagawa *et al.* suggested that risk factors for developing liver failure are severity of cirrhosis and a 60% or higher increase in baseline PVP after surgical occlusion of portosystemic shunts.[25] In the current study, we intended to ligate the portosystemic shunts with a less than 50% increase in baseline PVP after surgical occlusion of portosystemic shunts following splenectomy. In fact, 5-mmHg increases in PVP after ligation (increase of ~30% in baseline PVP) were eventually observed in case 4. We did not observe the development of esophageal variceal rupture or postoperative failure, irrespective of transient ascites, in our six cases. Even in the four patients in whom liver cirrhosis was revealed by biopsy, there were no episodes of postoperative liver failure or esophageal variceal rupture. Thus, surgical ligation of the portosystemic shunt following splenectomy may be feasible and safe, as long as the PVP at the clamping test of shunt vessels is not greater than 50% increase in baseline PVP. If clamp test of portosystemic shunts shows that PVP is more than 50% increase of the baseline PVP, some peripheral shunts could be ligated with a less than 50% increase in base line PVP as shown in case 4.

Liver function was classified as Child B in five out of six cases, and the increase in PVP after splenectomy followed by shunt ligation was mild (maximum, 5 mmHg). At present, the threshold at which increase in PVP after portosystemic shunt ligation increases the risk of esophageal variceal bleeding or the development of postoperative hepatic failure is unknown. Because this is a preliminary study, further examination is required to establish the indication, feasibility and effectiveness of this surgical ligation of the portosystemic shunt in combination with splenectomy for patients with hepatic encephalopathy. Furthermore, we should investigate if splenectomy is necessary in patients with normal PVP at the clamp test of portosystemic shunts.

In conclusion, splenectomy followed by surgical ligation of the portosystemic shunt may be feasible and safe for cirrhotic patients with portosystemic shunts who maintain relatively good liver function.

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