Biliary complications in the living donor

According to a survey of outcomes in 1508 living donors from five Asian centers, 15.8% had various complications, including 6.8% with bile leakage and 1.1% with biliary stricture.[33] In another survey, from the Japanese Liver Transplantation Society,[34] 11% of 1852 donors had biliary leaks and strictures; the majority of these complications occurred after right hepatectomy. Ten donors underwent surgical revision for biliary complications.

Conclusion

LDLT has gained a role even in western society to solve the problem of donor shortages. However, technical dilemmas still do exist, especially in regard to biliary reconstruction, as mentioned in this article. Further clinical trials are required to standardize the reconstruction procedure, and this should minimize the biliary complications after LDLT.

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Surgical technique

Anatomical and technical aspects of hepatic artery reconstruction in living donor liver transplantation

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Background. *We describe our experience with arterial reconstruction in living donor liver transplantation (LDLT) focusing on anatomic and technical aspects.*
Methods. *From June 1994 to February 2003, 132 grafts were implanted in 130 LDLT recipients including 1 re-transplant and 1 dual graft transplantation. Donor and recipient records were retrospectively reviewed. Anatomical variations in graft arteries were classified as: Type I, single pedicle with (Ia) or without (Ib) aberrant artery (left hepatic artery (HA) from left gastric artery or right HA from superior mesenteric artery); Type II, double pedicles with (IIa) or without (IIb) aberrant artery; Type III, equal to or greater than 3 pedicles. Statistical analyses were carried out using Mann-Whitney U-test.*
Results. *There were 72 male and 58 female recipients. The median age at transplantation was 3 years (range, 0.5 to 61). In left grafts, there were 34 Type Ia, 6 Type Ib, 33 Type IIa, 13 Type IIb, and 3 Type III; whereas in right grafts, there were 35 Type Ia, 6 Type Ib, 1 Type IIa, and 1 Type IIb. Two-in-one (2-in-1) segmental resection technique in graft HA harvest was carried out whenever there were tiny arteries supplying the donor graft. All HA reconstructions were done under microvascular techniques. There was no donor mortality and 1 recipient in-hospital mortality. There was no graft or patient loss due to HA occlusion. Donor complications included 3 biloma, 1 bile leak, 1 biliary stricture, and 1 late intestinal obstruction secondary to postoperative adhesions that were all successfully managed by non-operative interventions, except the biliary stricture that needed a revision to Roux-en-Y hepatico-jejunostomy. The 1-year and 5-year recipient survivals were 98% and 94%, respectively.*
Conclusions. *Successful HA reconstruction can be safely carried out in LDLT recipients and live donors with multiple graft arteries using the 2-in-1 segmental resection of donor HA under microvascular techniques. (Surgery 2006;140:824-8.)*

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Arterial reconstruction is a key point in successful living donor liver transplantation (LDLT). When comparing deceased donor liver transplantation utilizing whole liver grafts with LDLT, arterial reconstruction in LDLT is more difficult because a balance between recipient benefit and donor safety must be considered. There are limited surgical options that require several technical innovations. Our objective is to describe our experience with arterial reconstruction in LDLT focusing on anatomical and technical aspects.

PATIENTS AND METHODS

Patients. From June 1994 to February 2003, 131 LDLT were carried out in 130 recipients, including 1 re-transplantation, and 1 dual graft transplantation. A total of 132 grafts were implanted. There were 72 male and 58 female recipients (88 pediat-

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ric, 42 adult). The median age at transplantation was 3 years (range, 0.5 to 61). The indications for transplantation were biliary atresia (71), hepatitis B virus-related cirrhosis with or without hepatocellular carcinoma (26), hepatitis C virus-related cirrhosis with or without hepatocellular carcinoma (4), neonatal hepatitis (9), primary biliary cirrhosis (9), glycogen storage disease (6), Wilson's disease (2), Alagille syndrome (1), alcoholic liver cirrhosis (1), fulminant hepatic failure (1), and post-transplant graft failure (1). The living donors were mothers (56), fathers (25), sons (13), wives (13), aunts (5), brothers or sisters (5), grandmothers (3), husbands (3), cousins (3), nephew (1), niece (1), and father-in-law (1). Eighty-nine (89) recipients received left grafts (left lateral segment [51], extended left lateral segment [31], left lobe with the middle hepatic vein [MHV] [6], and left lobe without the MHV [1]), and 43 patients received right grafts (right lobe without the MHV [29], and right lobe with the MHV [14]). A total of 83 left-sided grafts and 5 right lobes were used for pediatric patients; and a total of 39 right lobes, 2 left lobes, and 1 dual graft were used in adults.

Preoperative evaluation. Conventional angiography was used to evaluate vascular anatomy preoperatively until 2000. Thereafter, non-invasive, single-modality diagnostic imaging using computed tomography (CT) angiography was used.[1]

Anatomical classification of graft artery. Anatomic variations in graft arteries were classified into 3 types according to the branching pattern of vessels that were identified during hilar dissection in donor operations. The types were: Type I, single pedicle with (Ia) or without (Ib) aberrant artery (left hepatic artery (HA) from the left gastric artery or right HA from the superior mesenteric artery); Type II, double pedicles with (2a) or without (2b) aberrant artery; and Type III, equal to or more than three pedicles (Fig 1).

Donor operation. The donor operation was described in detail previously.[2] During hilar dissection, the HA and portal vein were individually exposed and carefully divided. In left grafts, the proper HA was exposed up to the bifurcation of the left (or middle) HA and the right HA. In right grafts, the right HA was identified and isolated to the right side of the hepatic duct. The division point where the HA was to be divided was determined by the length and size of the artery, its relationship with the cutting plane of the liver, and the position of the arteries. In selected cases of Types II and III, segments of the proper HA that included the origins of multiple tiny arteries were taken to achieve a single orifice of adequate diameter size. This was defined as "2-in-1 segmental resection" (Fig 2).

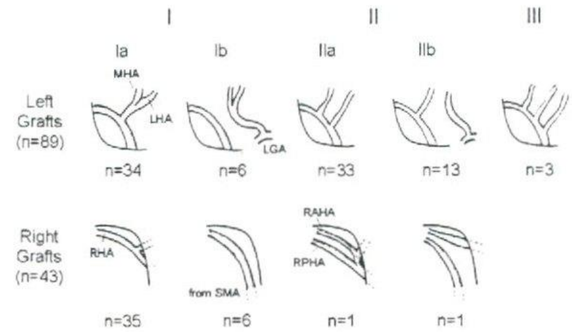

Fig 1. Anatomical classification of graft artery. LHA, left hepatic artery; MHA, middle hepatic artery; LGA, left gastric artery; RHA, right hepatic artery; SMA, superior mesenteric artery; RAHA, right anterior hepatic artery; RPHA, right posterior hepatic artery.

Recipient operation. In the recipient, the implanted graft was reperfused after reconstructing both hepatic and portal veins. After reperfusion, HA reconstruction was carried out under microvascular techniques. Whenever possible, end-to-end vessel anastomosis was done between recipient and graft HA using interrupted 9-0 monofilament nylon suture. In all cases, we used back wall-first approach using small vascular clips. This technique avoided vessel twisting during suturing. When multiple graft arteries were encountered, the dominant artery was reconstructed first. The dominant HA in grafts with multiple hepatic arteries was determined by comparing arterial flows during intraoperative Doppler ultrasonography (Acuson, Mountain View, Colo) after temporary occlusion of each artery in the donor operation using microvascular clips. This was followed by careful check on back-bleeding from the other arteries. If back-bleeding was sufficient, the unreconstructed arteries were ligated. After completing vessel anastomosis, blood flow was verified using color flow Doppler ultrasound.

In all cases, direct end-to-end vessel anastomosis was carried out. In Type I, a single anastomosis was carried out in all cases between graft and recipient arteries. Of 48 grafts in Type II (46 left, 2 right), 42 underwent a single anastomosis including 7 grafts with 2-in-1 segmental resection (6 left, 1 right); whereas 6 grafts (5 left, 1 right) received double anastomoses because of insufficient back-flow from the other arteries after anatomizing the dominant artery. In the 3 grafts with Type III, 2 grafts underwent a single anastomosis, whereas the third underwent double anastomoses due to the presence of

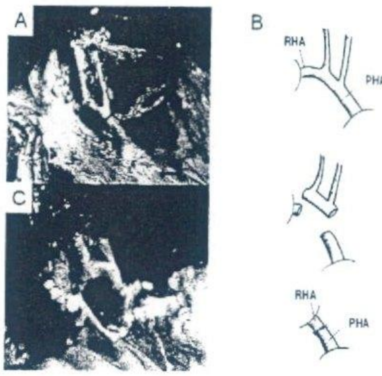

Fig 2. 2-in-1 Segmental resection in case of dual tiny arteries in left liver grafts. During donor operation, HA was transected at the point of proper HA (a) and right HA (b) (**A**). Remnant proper HA and the right HA were anastomosed under microscope (**B**). In the recipient, proximal end of the graft artery (proper HA) was anastomosed to recipient proper HA (arrow, **C**).

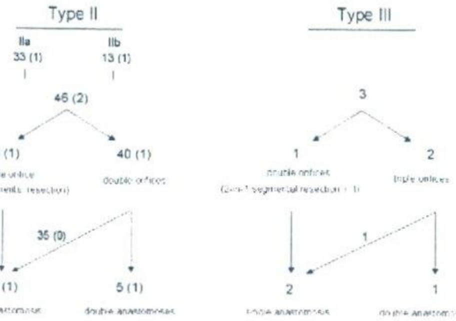

Fig 3. Techniques carried out in Type II and Type III liver grafts. The number of right grafts were put in parentheses.

double orifices after undergoing 2-in-1 segmental resection for 2 tiny arteries. Triple anatomizes was not carried out in any graft.

In 1 case of Type IIa, the HA reconstruction was complex because the recipient (LDLT 4) previously received deceased donor liver re-transplantation 6 years after primary LDLT where the HA anatomosis had been carried out utilizing the recipient common HA. During the second re-transplant utilizing a left graft from a living donor, the recipient right and left gastroepiploic arteries were used to anastomose with the graft middle and left HA, respectively.

Postoperative care and follow-up. Cyclosporine-based immunosuppression was used for pediatric recipients; whereas, tacrolimus-based immunosuppression was used for adults. Anti-coagulation was used utilizing continuous intravenous heparin infusion. Heparin was given at a dose of 200 U/ kg of body weight per day for a period of 14 days. Protease inhibitors and anti-thrombin III were not used post-operatively. In the recipients, daily color flow Doppler ultrasound was done to determine adequate blood flow and velocities during the first 2 weeks posttransplant, every other day on the third week, and twice a week thereafter until discharge. A diagnosis of vessel obstruction or thrombosis was initially made by Doppler ultrasound and confirmed by 3-dimensional CT angiography.

In donors who underwent 2-in-1 segmental resection of the hepatic arteries, a post-operative Doppler ultrasound was carried out on the second post-operative day and before discharge.

Statistical analyses. Statistical analyses were carried out using the Mann-Whitney *U*-test. A *P* value less than .05 was regarded as significant throughout the study.

RESULTS

Anatomical variations. In left grafts, there were 34 Type Ia, 6 Type Ib, 33 Type IIa, 13 Type IIb, and 3 Type III HA. In right grafts, there were 35 Type Ia, 6 Type Ib, 1 Type IIa, and 1 Type IIb HA noted (Fig 1). The incidence of multiple pedicles (Type II and III) was significantly higher in left grafts (49/89, 55.1% vs 2/43, 4.7%; $P < .01$). Of the 51 grafts with Types II and III, 2-in-1 segmental resection was carried out in 8 (15.7%) donors (7 left, 1 right) to achieve a single orifice of adequate diameter size. In the 8 donors, 5 underwent reconstruction of the HA using microvascular techniques between the remnant proper HA and the right or left HA (Fig 2). In the remaining 3 donors, reconstruction was not necessary due to the presence of aberrant HA that independently supplied blood to the remnant liver.

Forty-six percent (46/89) of left grafts and 97.7% (42/43) of right grafts exhibited a single HA orifice for anatomosis (Fig 3). The incidence of multiple orifices in graft artery was significantly higher in left grafts when compared with right grafts (48.3% vs 2.3%, $P < .01$).

Donor outcome. The mean donor follow-up period was 77.5 months (range, 6 to 126.6). There were a total of 6 donor complications. These included 1 bile leak, 3 biloma, 1 biliary stricture, and 1 late intestinal obstruction secondary to postoperative adhesions. All were successfully managed by non-operative interventions, except the donor who developed biliary stricture. This donor underwent Roux-en-Y biliary reconstruction. All donors are currently doing well and have returned to their

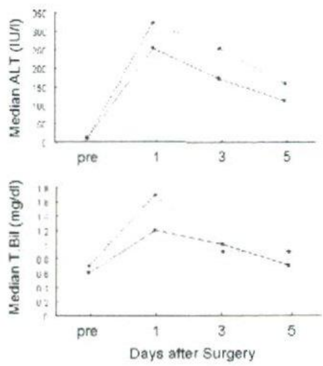

Fig 4. Liver function test results in left graft donors, with (broken line) or without (solid line) 2-in-1 segmental resection.

pre-operative activities of daily living. All complications occurred in donors who did not underwent 2-in-1 segmental resection of the HA.

The post-operative alanine aminotransferase in the 7 left graft donors who underwent 2-in-1 segmental resection of the HA was higher compared with the left graft donors who did not undergo the same resection but was not statistically significant. There was no statistically significant difference observed between the total bilirubin levels in the 2 groups (Fig 4). All 8 donors (7 left, 1 right) who underwent 2-in-1 segmental resection are currently doing well without complications (follow-up range, 3 to 32 months).

Recipient outcome. The mean recipient follow-up was 74 months (range, 6 to 126.6). The recipient 1-year survival was 98%, and the 5-year survival was 94%. There was no patient or graft loss due to HA occlusion. Hepatic artery occlusion requiring surgical revision was identified in 2 recipients at post-operative day 9 (LDLT 58) and day 12 (LDLT 97). Occlusion occurred in 1 left-side graft and 1 right-side graft. Both were detected by routine Doppler ultrasound examination before enzyme elevation. The causes of occlusion were HA thrombosis, and intimal dissection in the recipient HA. Both grafts were successfully rescued by re-anastomosing the HA. The left graft HA was anastomosed to the recipient common HA in the first and the right graft HA to the recipient right gastroepiploic artery in the second. These HA occlusions occurred in grafts that came from donors who did not underwent a 2-in-1 segmental resection of the HA.

DISCUSSION

Although LDLT is now an established therapeutic modality for end-stage liver disease in pediatric and adult patients, technical dilemmas still exist. With regard to arterial reconstruction, it seems that the approach has been well refined since the introduction of microvascular techniques.[3] In adult LDLT using right lobe grafts, where donor safety and small-for-size graft are debatable issues, the surgical anatomy and technique of HA reconstruction are simpler than those using left grafts as presented in this study. In our series, the 4.7% incidence of multiple graft arteries in right lobe grafts is similar to published reports.[4,5] Several studies show that pre-transplant angiography findings do not define clearly the surgical anatomy of the HA.[5,6] Our classification is based on findings at hilar dissection because the final decision depends on the intra-operative findings, and that conventional angiography is not always carried out in several institutions.[7]

In this series, we find that arterial reconstruction is more complex in LDLT using left grafts. This is due to a significantly greater incidence of multiple arteries in left grafts that require refinements in surgical technique as 2-in-1 segmental resection. Donor safety must be of paramount concern when doing this procedure. Although the incidence of arterial occlusion after reconstruction in the donor HA must be lower than the recipient, significant complications may occur. When encountering dual arteries during donor surgery, 3 options must be considered as previously mentioned. The first option is to divide the 2 arteries and reconstruct only 1. The second option is to divide the 2 arteries and reconstruct both. The third option is the 2-in-1 segmental resection of the HA. In most cases, the first and second options can be easily accomplished.[8] However, the use of tiny arteries carry the risk of thrombosis such that some transplant surgeons prefer not to use grafts with small arteries or dual arterial supply to liver segments 2 and 3.[9,10]

When deciding to carry out 2-in-1 segmental resection in a select case of multiple tiny arteries, the balance between donor safety and recipient benefit must be greatly considered. Size matching between graft artery and recipient artery must be done before any vessel division. Accurate judgment and meticulous surgical technique should be exercised whenever doing this procedure.

There were no significant differences in the liver function test results during the early postoperative period between the patients who underwent a standard HA procurement and those who underwent 2-in-1 segmental resection in this series. However, the alanine aminotranferase was higher in donors who underwent 2-in-1 segmental resection. This may be due to liver ischemia during HA reconstruction. So far, no donor complications were attributed to the 2-in-1 segmental resection of the HA in this series; but attention should be given to any donor with deteriorating liver function tests results.

If multiple tiny graft arteries are identified preoperatively, Dounard et al[11] introduced a novel approach with a 1-step strategy. First, they clipped smaller arteries via laparoscopic technique 1 week before the donor hepatectomy. In their experience, this allows an approximately 30% increase in the size of the remaining arteries that can be used successfully to carry out vessel end-to-end anatomosis. This approach is reasonable. It may not always be easy, however, to accurately evaluate the size of the artery during pre-transplant imaging.

Regarding surgical technique of arterial reconstruction, we used the back-wall first technique without rotating the anastomotic site in all cases. There are no reports comparing conventional technique with the back-wall first technique, however, several studies indicate an advantage of this procedure.[6,12] We believe that intimal injury can be reduced by this technique especially in cases where the HA is fragile due to age, liver disease, atherosclerosis or due to post-trans-catheter interventions like arterial embolization in hepatocellular carcinoma before transplant.

The 1.5% incidence of arterial occlusion after transplantation in this series is one of the lowest in literature. Prophylactic anticoagulation therapy is by intravenous heparin infusion only. Although HA thrombosis is not always due to technical causes,[13] we believe that when anatomosis is done correctly, no additional medication is necessary.

In conclusion, HA reconstruction in LDLT is more complex in left grafts when compared with right grafts due to a higher incidence of multiple arteries in the former. This problem can be overcome by meticulous peri-operative planning and intra-operative surgical innovations. The 2-in-1 segmental resection in the donor is technically demanding, but can be safely done by skilled microvascular surgeons. This technique should be considered for selected cases where multiple tiny arteries supply the graft.

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A Secured Technique for Bile Duct Division During Living Donor Right Hepatectomy

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Although biliary complication is well recognized as a significant factor affecting patient/graft morbidity, and the procedure and outcome of bile duct reconstruction in the recipient has been fully discussed,[1,2] the technical details of bile duct division in living donor hepatectomy have not yet been described. Especially in the case of right lobe living donor liver transplantation, the incidence of multiple bile ducts in the graft is high, up to 80% in previous reports,[3,4] and several studies have indicated that multiple bile ducts in the graft is a risk factor for biliary complication in the recipient.[5,6] Accordingly, we should cut the bile duct as close as possible to the common hepatic duct, but biliary stricture in the remnant liver of the donor is a great concern. To overcome these problems, we describe our technical inventions for safe and accurate bile duct division during living donor right hepatectomy.

During hilar dissection, the right hepatic artery and right portal vein are fully exposed and isolated from the hilar plate. At the final step of subsequent parenchymal transection, the right hilar plate is fully exposed and encircled with radiopaque marker filament, which is obtained from surgical gauze (Fig. 1). Intraoperative cholangiography is then performed via a catheter placed in the cystic duct (Fig. 2A). C-arm fluoroscopy is adapted during this procedure to enable us to check the optimal cutting point of the bile duct, which is made clear by pulling the filament and adjusting the accurate angle (Fig. 2B). The right hilar plate including the right hepatic duct is then sharply divided with scissors, and the stump of the remnant bile duct is closed with continuous 6-0 absorbable monofilament sutures ([Polydioxanone] Suture II, Ethicon, Somerville, NJ). Cholangiography with C-arm fluoroscopy is performed again to check the biliary leakage or stricture in the remnant bile duct (Fig. 2C). The right liver graft is then removed after the right hepatic artery, portal vein, and hepatic vein have been divided (Fig. 2D).

Of 54 living donor hepatectomies from August 1997 to December 2005, 38 underwent right hepatectomy, and the present procedure was adapted for use in the last 10 cases. Compared to the first 28 cases with ordinary cholangiography, the incidence of multiple ducts in the graft was significantly reduced (3/10 vs. 20/28, respectively; $P < 0.05$, Fisher exact test) without increasing donor morbidities. No biliary stricture developed in any of the donors. In regard to the incidence of biliary complications in the recipient, there were no significant differences between the 2 groups (30% vs. 29%, respectively).

These technical inventions for bile duct division during living donor right hepatectomy have enabled us to obtain the good quality of the bile duct with a single orifice and sufficient surrounding tissue, which may lead to reduced recipient biliary complications with further experience.

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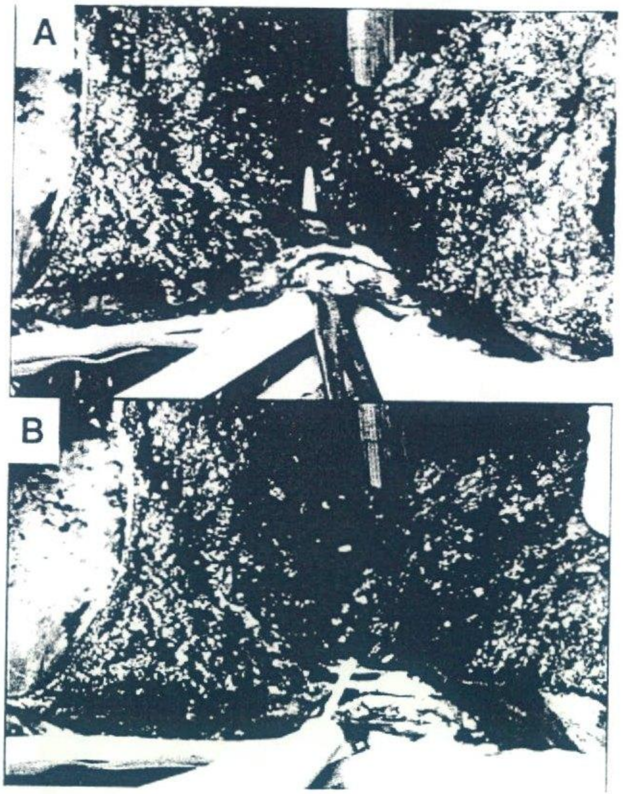

Figure 1. Encirclement of the hilar plate with radiopaque marker filament. (A) Isolation of the hilar plate by Kelley clamp. (B) The hilar plate is then encircled with radiopaque marker filament, which is obtained from surgical gauze.

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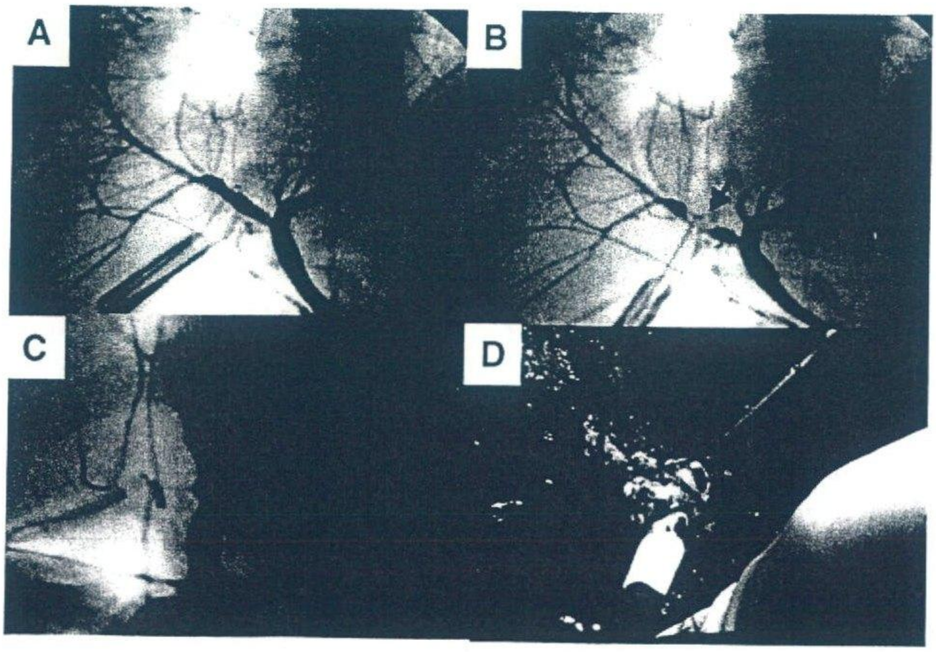

Figure 2. (A) Intraoperative cholangiography with C-arm fluoroscopy. (B) The radiopaque marker filament is pulled to show the cutting point of the bile duct (arrow). In this case, the hilar plate was cut around 2 to 3 mm away from the filament, toward the common hepatic duct. (C) There was no biliary leakage/stricture in the remnant bile duct after division. (D) The graft bile duct is obtained as a single orifice with sufficient surrounding tissue.

Excerpta Medica

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How I do it

Simplified technique for middle hepatic vein tributary reconstruction of a right hepatic graft in adult living donor liver transplantation

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Abstract

A simple procedure of direct end-to-end anastomosis between the middle hepatic vein tributary of the right hepatic graft and the preserved recipient middle hepatic vein is described. During the final step of total hepatectomy in the recipient, the middle hepatic vein was preserved, while crushing the liver tissue for a sufficient length of middle hepatic vein to perform tension-free anastomosis with the middle hepatic vein tributary of the graft. This procedure enabled us to avoid using an interposition graft.

Keywords: Liver transplantation; Living donor; Middle hepatic vein

In living-donor liver transplantation using a right lobe graft without the middle hepatic vein (MHV), the necessity of the reconstruction of a graft MHV tributary still is under debate [1–3]. Theoretically, it should be reconstructed to avoid graft congestion. The reason for hesitating to perform a reconstruction might be that it is a complex procedure using an interposition graft. Herein we describe a simple procedure of direct anastomosis between the middle hepatic vein tributary of the right hepatic graft and the preserved recipient middle hepatic vein.

Methods

During the final step of the recipient total hepatectomy, the common trunk of the middle and left hepatic vein was isolated and left, after dividing the right hepatic vein and the structure of the hepatic hilum, including the portal vein, hepatic arteries, and bile ducts. The confluence of the MHV into the inferior vena cava was identified, and the hepatic tissue surrounding the root of the MHV was crushed carefully with scissors longitudinally to expose the MHV. This maneuver was continued until the MHV was isolated at a sufficient length to create a tension-free anastomosis with graft MHV tributaries (Fig. 1). Meticulous ligation even for small branches of the MHV should be performed to avoid bleeding. After total hepatectomy was completed, the stump of the left hepatic vein (LHV) was closed with 4-0 prolene running sutures. To test for leakage from the MHV, it was flushed with heparinized saline from the stump and any leakage points were sutured with 5-0 or 6-0 Prolene (Ethicon, Inc, Somerville, NJ). After confirming that there was no leakage, the inferior vena cava was cross-clamped for hepatic vein reconstruction and the right lobe graft was inserted. After the right hepatic vein reconstruction had been completed, direct end-to-end anastomosis between the MHV tributary of the right lobe graft and the preserved recipient MHV was performed with 5-0 or 6-0 prolene running sutures (Fig. 2). The graft was perfused after subsequent portal vein reconstruction and the entire blood flow was checked with Doppler ultrasound after hepatic artery reconstruction.

After surgery, daily ultrasound was performed to confirm adequate outflow, and the MHV tributary still appeared patent at 2 weeks posttransplant, showing a biphasic wave form (Fig. 3). Thus far, we have performed this procedure in

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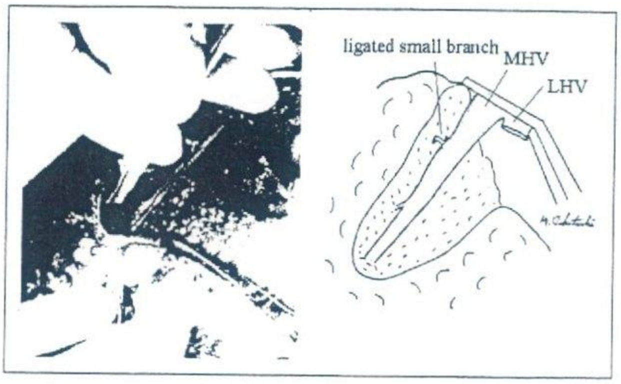

Fig. 1. MHV isolation. The liver tissue surrounding the recipient MHV was crushed with scissors longitudinally to a length sufficient for tension-free anastomosis. LHV, left hepatic vein.

2 cirrhotic patients, a 65-year-old man with hepatitis B virus, and a 50-year-old man with hepatitis C virus, neither of whom had any hepatocellular carcinoma. The former patient died of sepsis 1 month after transplantation with patent MHV tributary, and the latter patient was doing well with good liver function at the time of this report 1 year after transplantation.

Comments

In adult-to-adult living-donor liver transplantation, the key to success is taking a hepatic graft with adequate functional volume. Even when the actual volume in weight appears to be enough, we occasionally encounter a situation in which functional volume is smaller than expected owing to several kinds of graft injuries. Congestion of the right paramedian sector (segments V and VIII according to Couinaud's nomenclature) caused by lack of reconstruction of the MHV tributaries is well recognized as one of the main possible causes of injury of right lobe graft without the MHV [4]. Although several studies showed that reconstruction of MHV tributaries should not be necessary because final patient/graft outcome in such cases appeared to show no significant difference from that in cases without reconstruction [3], graft congestion might lead to prolonged jaundice and ascites, a so-called *small-for-size syndrome*, at an early posttransplant period [5], which also can affect prolonged hospital stay. The reason for hesitating to undertake reconstruction might be the fact that it is a complex procedure using an interposition graft [6,7]. Accordingly, when the simpler procedure is available, we propose that in any patient at least the main MHV tributary should be reconstructed. This type of anastomosis has been mentioned in passing before [8]. Our procedure in the present study may be simpler than that of using an interposition graft. Anastomosis is single, and it is not necessary to take the vein graft. Theoretically, we can obtain the MHV with the original length of it in the liver (even 10 cm or longer), although it depends on the quality of the MHV. The length of time required to extract the MHV was a few minutes. Crushing with scissors was useful for quick isolation of the MHV and, if paying careful attention, it does not cause injury. However, further discussion is recommended to determine whether this technique can be adapted for use in cases of malignant liver tumors (thus far there appear to be contraindications), and further technical innovations should be made in cases with multiple significant MHV tributaries in the graft or with size-mismatched ones, in which reconstruction with a single recipient MHV alone might not be possible. In such cases, the recipient LHV and/or big recipient MHV tributaries may be usable.

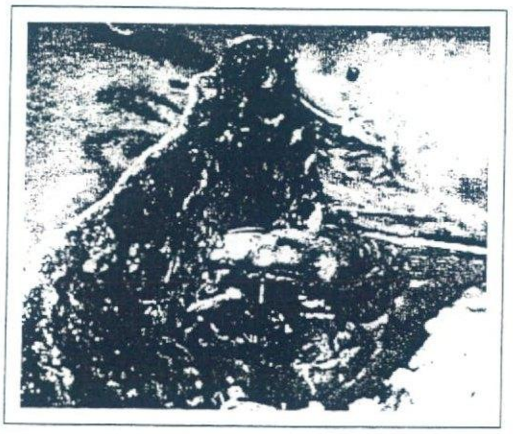

Fig. 2. Direct end-to-end anastomosis between the preserved recipient MHV and the graft MHV tributary.

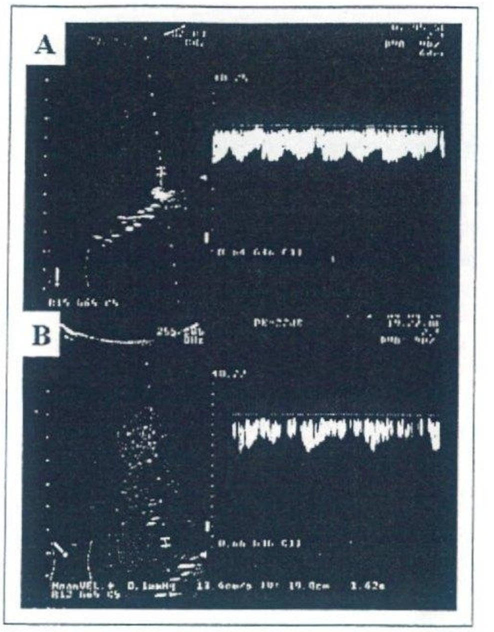

Fig. 3. Blood flow of reconstructed MHV tributary (**A**) just after reperfusion and (**B**) at 2 weeks after surgery.

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CASE REPORT

A case of mucin producing liver metastases with intrabiliary extension

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Abstract

A 75-year-old man was admitted to our hospital with a diagnosis of liver metastases from colon cancer. He underwent right hemicolectomy for cecal cancer eight years ago, and had a metastatic liver tumor in segment 8 (S8), which was surgically resected about 4 years after the initial operation. Histopathological examination of the resected specimens from both operations revealed a well-differentiated adenocarcinoma with mucinous carcinoma. Four months after the second operation, computed tomography demonstrated a low-density lesion at the cut surface of the remnant liver. Although it was considered to be a postoperative collection of inflammatory fluid, it formed a cystic configuration and increased in size to approximately 5 cm in diameter. With a tentative diagnosis of a recurrence of metastatic cancer, partial hepatectomy of S8 was performed. Histological examination of the resected specimens also revealed mucinous adenocarcinoma, which had invaded into the biliary ducts, replacing and extending along its epithelium. Immunohistochemically, the tumor cells were positive for cytokeratin (CK) 20, but negative for CK7. Therefore, the tumor was diagnosed as a metastatic adenocarcinoma from colonic cancer. Liver metastases of colorectal adenocarcinoma sometimes invade the Glisson's triad and grow along the biliary ducts.

Key words: Liver metastases; Mucin; Intrabiliary extension; Cytokeratin 7; Cytokeratin 20

Tokai H, Kawashita Y, Eguchi S, Kamohara Y, Takatsuki M, Okudaira S, Tajima Y, Hayashi T, Kanematsu T. A case of mucin producing liver metastases with intrabiliary extension. *World J Gastroenterol* 2006; 12(30): 4918-4921

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INTRODUCTION

Liver metastases can occur in 25%-35% of patients with colorectal carcinoma[1], and surgical resection has become accepted as a reasonable treatment for patients with liver metastases. However, because of their propensity to spread along epithelial surfaces, liver metastases of colorectal carcinoma sometimes invade the Glisson's triad[2]. Therefore, in contrast to hepatocellular carcinoma (HCC), bile duct invasions of liver metastases from colorectal carcinoma are seen in about 10%-12% of resected liver metastases[3,4]. On the other hand, cystic formation caused by mucin producing metastatic tumor from colorectal cancer has only rarely been reported. Here, we report a case of mucin producing liver metastases with intrabiliary extension that was difficult to distinguish from benign cystic change.

CASE REPORT

A 75-year-old man was admitted to our hospital with a liver tumor. He underwent right hemicolectomy following a diagnosis of cecal cancer in January, 1994. Histological examination of the resected specimens revealed a well-differentiated adenocarcinoma with mucinous carcinoma, which invaded the subserosal layer and metastasized to regional lymph nodes. Four years after his initial operation, he underwent partial hepatectomy of segment 8 (S8) due to a diagnosis of metastatic liver tumor on June 22, 1998. Histopathological examination of the resected specimens revealed a well-differentiated adenocarcinoma with mucinous carcinoma, similar to cecal cancer. The tumor invaded only the bile duct, but surgical margin was negative for cancer. Four months after his second operation, abdominal computed tomography (CT) revealed a low-density lesion at the cut surface of the liver. Initially, it was considered to be a postoperative collection of inflammatory fluid. Through the continuous observation using periodical CT scans, the low-density lesion gradually formed a cystic mass over two years, but little change was found in size. Two years later, the mass increased in size

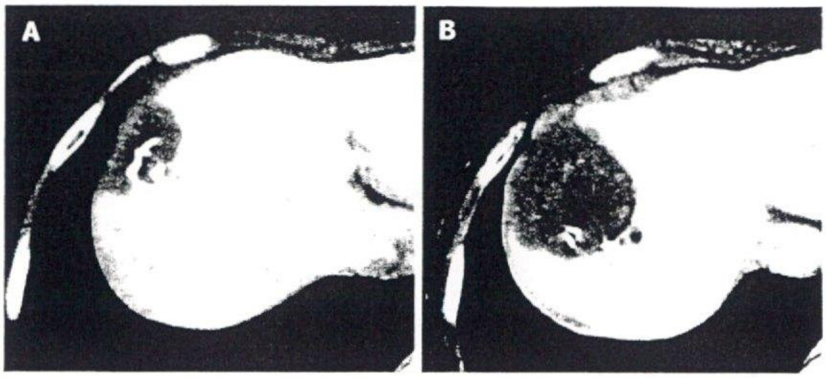

Figure 1 A low-density lesion at the cut surface of the liver in December, 1998 (**A**) and two years later, the mass increased in size to approximately 5 cm in diameter (**B**).

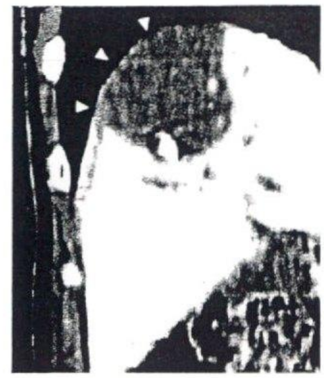

Figure 2 A low-density cystic tumor in S8 with local dilatation of the IHBD (arrows). The tumor was bordered by the diaphragm (arrow heads).

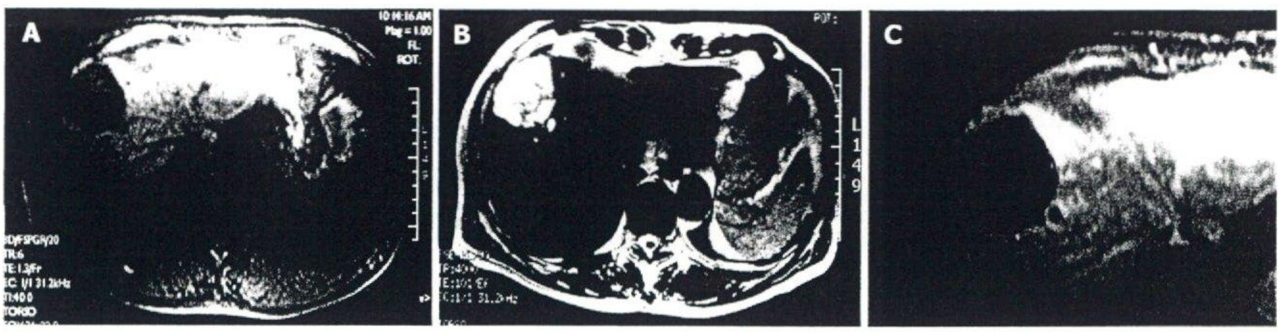

Figure 3 A low intensity signal on T1-weighted (**A**) and a high intensity signal on T2-weighted (**B**) images. The edge of the tumor was slightly enhanced by gadolinium, while the inside was heterogeneous (**C**).

to approximately 5 cm in diameter (Figure 1). Cytological examination from ultrasonography (US)-guided fine needle aspiration biopsy revealed it to be class III, indicating a borderline malignancy.

On admission, the patient exhibited no abnormal findings upon physical examination. Complete blood counts and serum chemistries were within normal limits. Among tumor markers, serum carcinoembryonic antigen (CEA) levels and alpha-fetoprotein (AFP) levels were within normal limits. The indocyanin green retention rate after 15 min (ICG R15) was 16.0%. Abdominal CT revealed a low- density cystic tumor of S8 that measured about 4 cm × 5 cm in size, with local dilatation of intrahepatic bile ducts (IHBD). The tumor was bordered by the diaphragm (Figure 2). Abdominal magnetic resonance imaging (MRI) revealed a tumor with a low intensity signal on T1-weighted images and a high intensity signal on T2-weighted images (Figures 3A and B). In addition, the edge of the tumor was slightly enhanced by gadolinium, while the inside was heterogeneous (Figure 3C). Magnetic resonance cholangiopancreatography (MRCP) revealed local dilatation of IHBD. Based upon these examinations, one of the differential diagnoses was biloma at the cut end of the previous hepatectomy. To further investigate the content of the tumor, US-guided biopsy was performed. An aspirated sample contained a small volume of yellow and clear fluid, but bile was not found. Histological examination of the biopsy specimens revealed a mucinous adenocarcinoma. Finally, the tumor was judged to be a recurrence of metastatic cancer with invasion to the IHBD. There was no evidence of metastasis in any other organs or in regional lymph nodes. The patient was considered to be a candidate for surgery. On March 13 in 2002, he underwent the third operation. When the peritoneal cavity was entered, there was no evidence of peritoneal dissemination, enlarged lymph nodes or ascites. The tumor was located in the liver in S8 adhering to the diaphragm and was about 4 cm in diameter, as measured by US. US was also performed to indicate a sufficient surgical margin of at least 15 mm. The tumor was resected using intermittent clamping of the primary branch of Glisson's triad (Pringle's procedure). When we cut the regional Glisson's triad, mucinous bile was found at the cut end of the bile duct. The portal vein was intact. According to the preoperative informed consent, partial resection of the liver in sub-segment 8 and the diaphragm was performed. Histological examination of the resected specimens revealed a well-differentiated mucinous adenocarcinoma, which was consistent with the metastatic lesion from colon cancer. The tumor extended along the lumen of the biliary ducts, replacing the non-neoplastic epithelium (Figure 4). The peripheral bile ducts were obstructed by the cancer cells, and the cut end of the bile duct was positive for cancer. The tumor invaded only the abdominal side of the diaphragm and was not apparent on the thoracic side. Immunohistochemically, the tumor

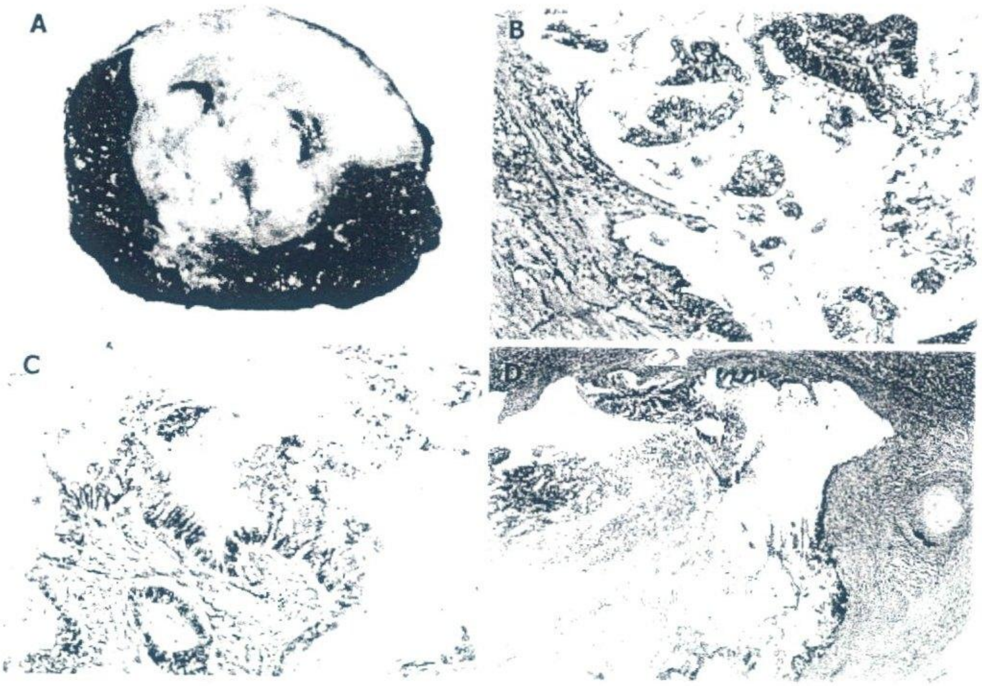

Figure 4 Macroscopic finding (**A**), well-differentiated mucinous adenocarcinoma (**B**) similar to cecal cancer (**C**), extension of tumor cells along the lumen of the biliary ducts with the non-neoplastic epitheliumreplaced (**D**). (B) HE, × 100; (C) HE, ×100; (D) HE, ×18.

Figure 5 Immunohisotochemically, tumor cells positive for CK 20 (**A**), but negative for CK7 (**B**), normal epithelial cells of IHBD positive for CK7 (arrow). (**A**) ×100; (**B**) ×100.

cells were positive for CK 20, but negative for CK7 (Figure 5). Thus, we diagnosed it as a recurrence of metastatic adenocarcinoma from cecal cancer.

Three months after the hepatectomy, the patient exhibited a recurrence at the cut surface of the residual liver. He and his family did not hope further surgery. Although he received chemotherapy using 5-FU for the local recurrence, he died 2 years and 9 mo after the second hepatectomy.

DISCUSSION

Liver metastases occur in 25%-35 % of patients with colorectal cancer[1]. Surgical resection has become a recognized curative treatment[1,5,6]. However, the rate of intrahepatic recurrence has been reported to range from 16% to 28%[5,7], and 9%-25% of these arise at the surgical margin[8,9]. Okano *et al*[3] reported that 42% of patients who have undergone hepatectomy for colorectal liver metastases exhibit bile duct invasion, 12% of which exhibit macroscopic invasion. Among these metastases, an intrabiliary extension pattern is rare. Kubo *et al*[4] reported that 3.7% of resected colorectal liver metastases are extended predominantly along the bile duct without forming an extrabiliary mass. The prognosis of patients with macroscopic bile duct invasion is better than that of patients with microscopic intraluminal invasion, which tends to aggressively involve the Glisson's triad[3,4].

In the present case, we initially considered the cystic lesion to be a post-operative collection of inflammatory fluid. However, the lesion turned out to be a cystic tumor including mucin produced by the remnant cancer cells. Cancer cells and mucin obstructing the IHBD, caused dilatation of the peripheral bile ducts. Microscopically, about 10% of metastatic tumors from colorectal carcinoma exhibit mucinous features[10]. Furthermore, the frequencies of incidence of localized IHBD dilatation caused by metastatic liver cancer and cystic degeneration of metastatic tumor have been reported to be 6%[11] and 2%-4%, respectively[12,13]. Therefore, the present case was considered to be a very rare case and preoperative diagnosis could not be confirmed by imaging examination alone. On the other hand, it is known that cholangiocellular carcinoma (CCC) is often accompanied with dilatation of the IHBD, because intrahepatic CCC exhibits bile duct extension, either through infiltration into the periductal tissues or appearing as a cast-like growth into the ductal lumen[14]. Furthermore, CCC sometimes exhibits mucin production. Thus, the growth of colorectal metastases with bile duct invasion can be indistinguishable from that of less aggressive CCC, and it is sometimes difficult to make a differential diagnosis histologically. To discriminate liver metastases from primary CCC, immunostaining for CK7 and CK20 can be very useful. A CK20-positive and CK7-negative pattern is highly characteristic of liver metastases from colorectal cancer, compared with most adenocarcinomas including CCC that are usually CK20-negative and CK7-positive[15-17]. In the present case, this immunohistochemical finding allowed us to make a definite diagnosis.

Our patient has survived for more than two-years, in spite of local recurrence. This may be a consequence of the less aggressive features of this tumor, which exhibits macroscopic bile duct extension[3,4]. However, because this invasion pattern tends to make the cut ends positive for cancer cells, it appears that it is necessary to examine the cut end of Glisson's triad by stamp cytology or frozen section pathology. Actually, during the 2nd hepatectomy, mucinous bile was found in the bile duct. However, since the tumor was a metastatic colorectal cancer rather than a CCC, partial hepatectomy was a procedure of choice for us. For colorectal metastases, we usually perform partial hepatectomy with a sufficient margin rather than anatomical resection if possible. Recently, Pawlik *et al*[9] reported that the width of a negative surgical margin does not affect survival, recurrence risk, or site of recurrence. However, after having experienced our present case, anatomical hepatic resection may be a treatment of choice for metestatic liver tumor with bile duct extension to avoid the potential for a positive surgical margin. Further studies are necessary to develop a suitable surgical procedure for this unusual pattern of liver metastasis.

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CASE REPORT

Destructive granuloma derived from a liver cyst: A case report

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Abstract

We herein report the case of an idiopathic liver cystic mass which aggressively infiltrated the thoraco-abdominal wall. A 74-year-old woman who had a huge cystic lesion in her right hepatic lobe was transferred to our hospital for further examinations. Imaging studies revealed a simple liver cyst, and the cytological findings of intracystic fluid were negative. She was followed up periodically by computed tomography (CT) scans. Seven years later, she complained of a prominence and dull pain in her right thoraco-abdominal region. CT revealed an enlargement of the cystic lesion and infiltration into the intercostal subcutaneous tissue. We suspected the development of a malignancy inside the liver cyst such as cystadenocarcinoma, and she therefore underwent surgery. A tumor extirpation was performed, including the chest wall, from the 7th to the 10th rib, as well as a right hepatic lobectomy. Pathologically, the lesion consisted of severe inflammatory change with epithelioid cell granuloma and bone destruction without any malignant neoplasm. No specific pathogens were evident based on further histological and molecular examinations. Therefore the lesion was diagnosed to be a destructive granuloma associated with a long-standing hepatic cyst. Since undergoing surgery, the patient has been doing well without any signs of recurrence.

Key words: Destructive granuloma; Liver cyst

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INTRODUCTION

A liver cyst is a common lesion that tends to be mostly asymptomatic, however, once it is associated with other events such as bleeding, infection and rupture, it often becomes symptomatic and treatment is thus usually needed. Granulomas can be seen in any part of the body and they reflect a host inflammatory responses elicited by a wide variety of stimuli[1,2], however, it is uncommon that a granulomatous reaction develops in a liver cyst[3].

We experienced the case of highly destructive, non-malignant, granulomatous lesion that originated from a long-standing hepatic cyst that infiltrated the thoraco-abdominal wall mimicking hepatic cystadenocarcinoma. To the best of our knowledge, this is the first known occurrence of a case of a hepatic granuloma that developed secondary to a liver cyst with a highly invasive capacity.

CASE REPORT

A 73-year-old Japanese woman presented at our hospital with right. hypochondralgia on September 1997. Computed tomography (CT) showed a huge liver cyst measuring 10cm in the right lobe of the liver without any solid component (Figure 1A). Subsequently, 2.4L of serous fluid were percutaneously drained, without any sclerosing agent administered into the cyst. A cytological examination of the aspirated fluid was negative for neoplastic cells. Since her symptom had subsided after the fluid drainage, she was carefully followed-up without any further treatment. On May 2003, she was again referred to us with abdominal distention and pain in the right thoraco-abdominal region. The results of laboratory tests showed slight elevations in the C-reactive protein (CRP) level (0.5mg/dL, normal range < 0.17). Serological tests for hepatitis B and C virus were negative. The serum levels of carcinoembryonic antigen, carbohydrate antigen 19-9 and α-fetoprotein were all within the normal ranges. Other tests including her liver function were within the normal limits. A CT scan showed a cyst in the right. lobe of the liver similar to the one observed 6 years previously. In addition, a calcified lesion was also found around the cyst (Figure 1B). An axial and coronal view of an MRI showed a multilocular cyst with a thick wall and solid component extending into the subcutaneous tissue (Figure 2A and B). MR cholangiopancreatography demonstrated no dilatation in the biliary system, thus indicating that there was most likely no communication with the liver cyst (Figure 2C). These findings closely resembled hepatic cystadenocarcinoma.

After admission, the cystic tumor gradually increased

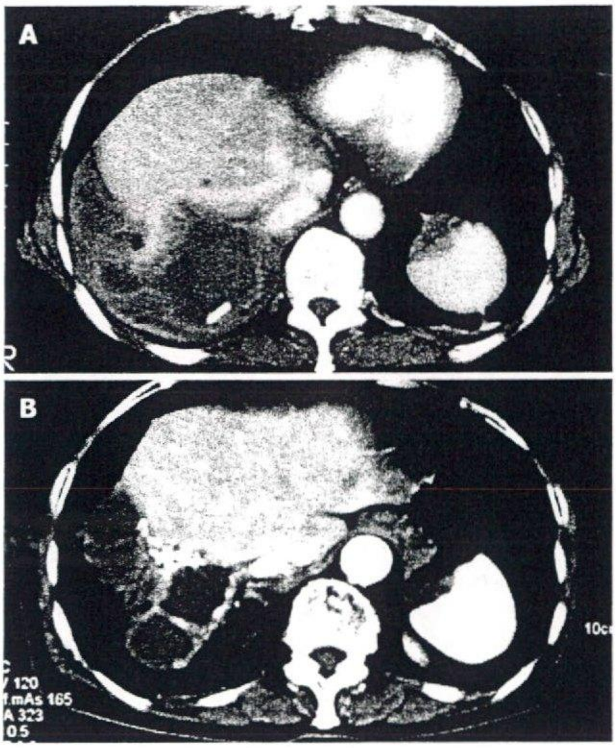

Figure 1 Computed tomography revealed a huge multilocular cyst measuring 10 cm in the right lobe of the liver on September 11th, 1997 (**A**). A similar cyst with a calcified lesion was found in the right lobe of the liver on May 15th, 2003 (**B**).

in size and finally her skin above the invasion site became reddish and swollen (Figure 2D), thus suggesting malignant tumor invasion. After obtaining the patient's informed consent, we performed an *en bloc* resection of the hepatic right lobe including the whole cyst, along with the diaphragm, rib bone, and skin. After completing the resection, the defect of the diaphragm was covered with the great omentum, and the thoraco-abdominal wall defect was reconstructed using a musculo-cutaneous flap including the anterior sheath and the left rectus abdominis muscle which both receive the blood supply from the superior abdominal artery (Figure 3A and B). Macroscopically, the cystic tumor directly invaded the intercostal space through the diaphragm (Figures 4A and 4B). No microorganism was found in the cyst fluid or the resected materials according to the results of microbilological culture examinations. A pathological examination revealed that the bone had been destroyed by the invasion of the granuloma, which was composed of epithelioid cells with necrotic areas (Figure 4C). No malignancy or microorganism was detected in any tissue samples. Because the histology was similar to tuberculosis, Ziehl-Neelsen staining and DNA-PCR using three different primers for a tubercle bacillus were performed with negative results. Hepatic hydatid disease was excluded by the fact that she had no history of living or traveling to the epidemic area such as Hokkaido prefecture in Japan and her blood samples did not show the presence of the antibodies against ehinococcus. From these findings, the cystic tumor was therefore histologically diagnosed to be a hepatic epithelioid granuloma. (Figure 4D)

The patient had an uneventful postoperative course and was discharged on postoperative day 27. She remains asymptomatic until 24 mo postoperatively, without any signs of recurrence.

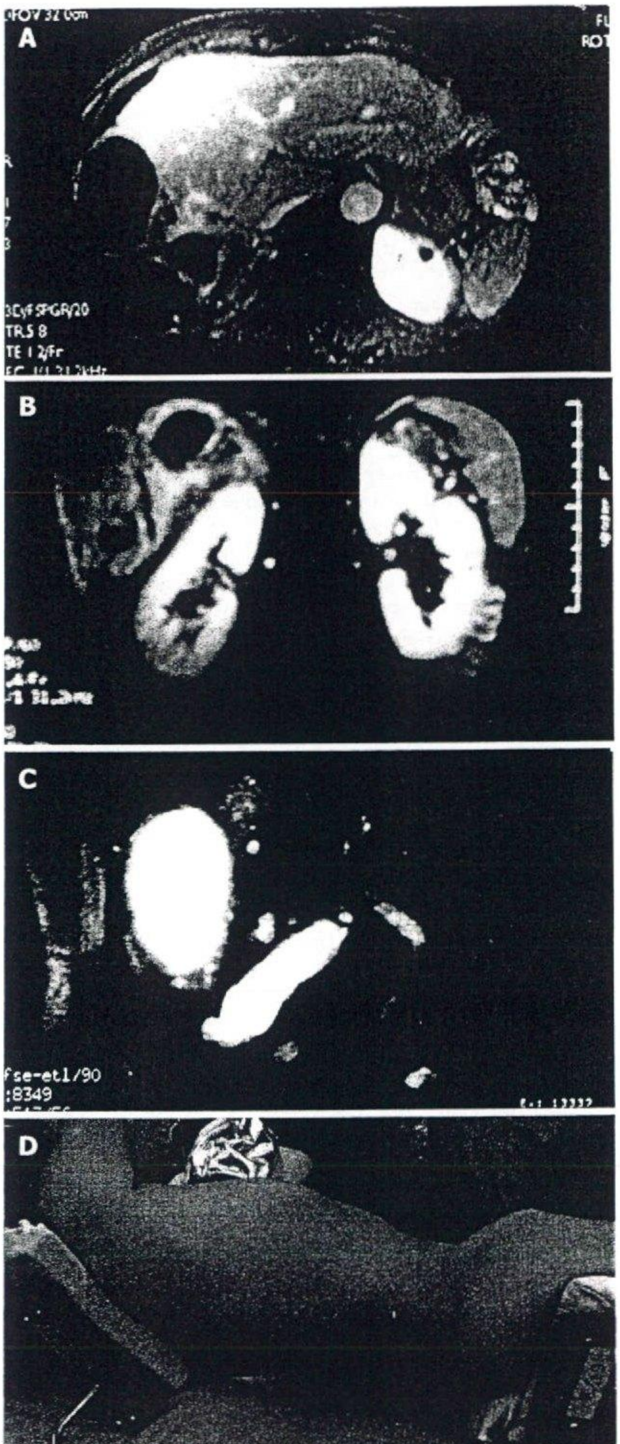

Figure 2 An axial (**A**) and coronal (**B**) view of magnetic resonance imaging (MRI) showed a multilocular cyst with a thick wall with a solid component extending into the subcutaneous tissue. MR cholangio-pancreatography showed no dilatation in the biliary system, and most likely no communication with the liver cyst (**C**). The skin showed red swelling by the subcutaneous extension of the hepatic cyst (**D**).

DISCUSSION

There has been a great progress in the diagnostic modali-

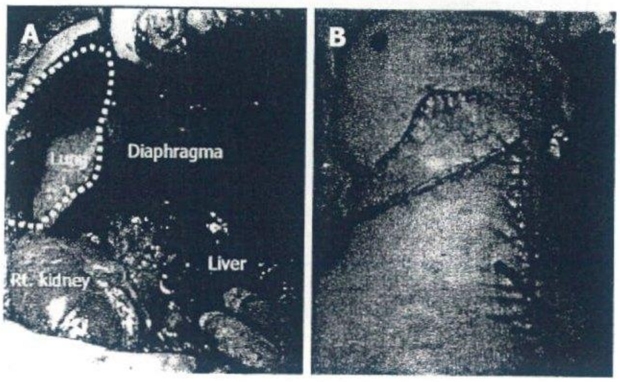

Figure 3 An en bloc resection resulted in a huge defect (**A**, yellow dotted circle). The defect of the diaphragm was covered with the great omentum, and the thoraco abdominal wall defect was reconstructed by a musculo-cutaneous flap including the anterior sheath and the left rectus abdominis muscle which both receive the blood supply comes from the superior abdominal artery (**B**).

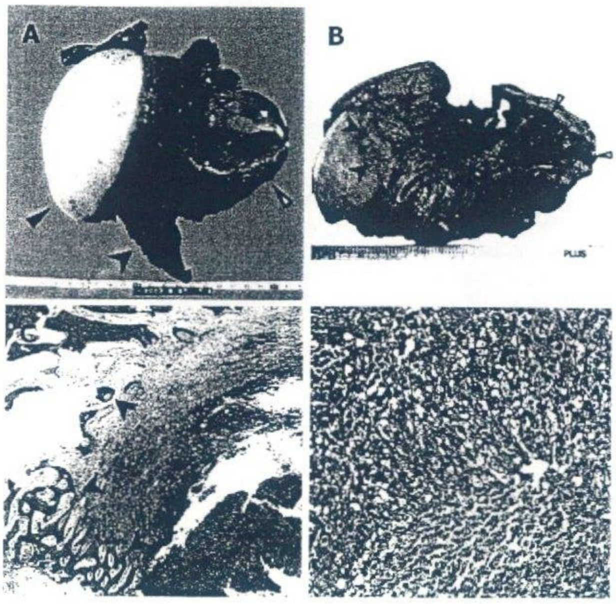

Figure 4 Macroscopically, the cystic mass directly invaded the intercostal space through the diaphragm (**A**. Resected crude specimen, black triangle; skin, black arrow head; ribs, white triangle; cystic tumor; **B**. Cut surface of the specimen, black arrow head; subcutaneous invasion, white triangle; cystic tumor). Microscopically, the bone was destroyed by an invasion of granuloma tissue (**C**). The granuloma was composed of epithelioid cells with necrotic areas (**D**).

ties for hepatic lesions including ultrasonography, CT, magnetic resonance imaging (MRI) and angiography[4]. Cystic lesions of the liver, which occupy a large part of hepatic lesions and are seen in up to 5% of the population, can be classified as developmental, neoplastic, inflammatory, or miscellaneous lesions. If a solid component develops inside the cyst, the possibility of a malignant transformation should be considered[5]. However, even routine imaging procedures such as CT or MRI generally fail to differentiate hepatic granulomas from other neoplasms[2].

Aspiration cytology can help in making a preoperative diagnosis, however, it is sometimes difficult to accurately hit the target tumor under US guidance, and this procedure also carries a risk of potentially causing needle-track and peritoneal seeding if the lesion is a malignant tumor[6, 7].

A wide variety of underlying conditions such as sarcoidosis[8], malignant lymphoma[9], tuberculosis[2], and HCV infection[10,11] can cause hepatic granulomas, with resulting prognostic and therapeutic implications. However, the histological features of such granulomas are not distinctive, while a specific etiological agent often cannot be identified despite serological, immunological microbiological, and radiological investigations, thus often resulting in a diagnosis of "idiopathic" hepatic granulomas. Although the exact etiology and pathogenesis of this aggressively infiltrating granuloma seen in the present case remains unclear, we speculated that an unidentified organism infection possibly occurred via two different routes: (1) the endogenous route, via the blood stream; (2) the exogenous route: a reverse infection through a drainage catheter when aspiration had previously been performed.

A spontaneous regression occurs in some cases of hepatic granulomas, therefore, patients can be treated by simple observation or conservative therapy with anti-inflammatory drugs including antibiotics or steroids in most cases. In the present case, the fact that destroyed and necrotic tissue caused inflammatory reactions suggested that empirical antibiotic therapy would be ineffective, to make matters worse, such conservative treatment could have possibly induced the development of such antibiotic-resistant bacteria as Methicillin-Resistant Staphylococcus Aureus (MRSA). In addition, steroid treatment is generally effective for sarcoidosis, however, it risks exacerbating tuberculosis and an earlier paper described a patient who died from miliary TB after the administration of empirical steroids [12].

Great improvements in operative techniques, perioperative patient management, and patient selection criteria have not made a hepatic resection one of the standards and effective methods for liver cysts[13]. As a result, a hepatectomy is recommended for cystic lesions when a tumor of the liver with a potential malignancy cannot be ruled out[14,15].

In the present case, the clinical course in which a solid component developed during the follow-up of a liver cyst, while infiltrating into the subcutaneous tissue with the destruction of the ribs was highly suggestive of the development of a malignancy, such as cystadenocarcinoma. The pathological diagnosis turned out to be a cancer-free lesion, namely, benign granuloma. Despite the highly invasive capacity of this lesion, the good clinical outcome in this case supports the suitability of a hepatic resection with the total removal of the affected areas as the treatment of choice.

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