รายงานผู้ป่วย

The first human orthotopic liver transplant in Thailand : a case report

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On November 28, 1987, the first successful human liver transplantation in Thailand was performed at Chulalongkorn Hospital. The recipient was a 63-year-old patient suffering from a large hepatocellular carcinoma of the right liver lobe associated with posthepatitic cirrhosis. His blood group was AB, RH+. The liver allograft was harvested from a cadaveric donor whose blood group was B, Rh+. The operation took 5 hours and required 4 units of blood transfusion. Postoperative recovery was satisfactory with good graft function. He was discharged from the hospital after 33 days and was doing well at the last followup, 6 weeks after surgery.

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รายงานนี้เป็นรายงานการผ่าตัดปลูกถ่ายตับในผู้ป่วย ซึ่งได้กระทำสำเร็จเป็นครั้งแรกในประเทศไทยที่โรงพยาบาลจุฬาลงกรณ์ เมื่อวันที่ 28 พฤศจิกายน 2530 ผู้ป่วยเป็นชายไทยอายุ 63 ปี หมู่เลือด AB Rh+ ซึ่งป่วยเป็นโรคมะเร็งเซลล์ตับขนาดใหญ่ในตับกลีบขวา ร่วมกับตับแข็งที่เกิดภายหลังไวรัสตับอักเสบ ผู้ป่วยได้รับการผ่าตัดเอาตับออกทั้งอัน และรับการปลูกถ่ายตับจากผู้เสียชีวิตซึ่งมีหมู่เลือด B Rh+ การผ่าตัดใช้เวลาประมาณ 5 ชั่วโมง ผู้ป่วยได้รับการถ่ายเลือดรวมทั้งสิ้น 4 ยูนิต หลังผ่าตัดผู้ป่วยฟื้นตัวจากการผ่าตัดได้ดี ตับใหม่ที่ได้รับทำงานได้อยู่ในเกณฑ์ดี และผู้ป่วยสามารถกลับบ้านได้ในเวลา 33 วันหลังผ่าตัด การติดตามผู้ป่วยเมื่อ 6 สัปดาห์หลังผ่าตัด ผู้ป่วยอยู่ในสภาพที่น่าพอใจ

Since Thomas E. Starzl successfully performed the first orthotopic liver transplant in human in 1963,[1] initial progress in this field had been slow to develop. It took him another four years before he did more successful cases with appreciably extended survival[2] But despite this early glimpse of hope for patients with endstage liver disease, the reported average one-year survival of 30% could hardly justify the expenses and efforts required in performing the procedure outside a few "specialized" transplant centers in the world[3] More than a decade went by, during which the perseverance and courageous foresight of such great liver transplant pioneers, such as Thomas E. Starzl in the U.S.A. and Roy Y. Calne in the U.K. among others, were put into perfecting the procedure. It was not until the late 1970's that, with the discovery of cyclosporin A,[4] better anesthesia and surgical technics, and multi-drug immunosuppressive regimens, liver transplantation gradually transcended to a state of realistic surgery in the treatment of endstage liver disease. With an average one-year survival rate of better than 60%, the early 1980's dawned a new era of liver transplantation.[5] The endorsement of the procedure by the National Institute of Health Concensus Development Conference, held in July 1983,[6] fostered the cropping up of "new" liver transplant centers, which by now number more than 100 worldwide, almost overnight.

In Thailand, initial effort at whole organ transplantation began with the first successful kidney transplant performed at Chulalongkorn Hospital in 1972[7] Unfortunately, the prohibitive costs and efforts required, and particularly the lack of legislative support of standard brain death criteria, have significantly impeded a proper growth rate in the utilization of the procedure and the field of whole organ transplantation in general. However, recent reports of promising results of liver transplantation in the western literature have refreshed interests among transplant centers in the country. Thus in July 1987, Vithya Vathanophas et al from Siriraj Hospital, were the first to report the feasibility of orthotopic liver transplantation in a series of experimental animals at the twelfth annual congress of the Royal College of Surgeons of Thailand.[8] Meanwhile, another transplant team led by Visist Dhitavat at the Department of Surgery, Chulalongkorn Hospital, was organized. Four months later, on November 28, 1987, the team successfully performed the first human liver transplant in Thailand. The following case report describes the detail of this experience.

CASE REPORT

C.P. was a 63-year-old Thai male farmer from Ayudhya province, who was referred to Chulalongkorn Hospital on October 20, 1987, with a one-month history of malaise, anorexia and 6-kg weight loss. Ten days prior to admission, he began to experience discomfort in the right upper quadrant of the abdomen on deep inspiration and coughing. Past medical history was unremarkable. He denied regular alcoholic consumption as well as history of hepatitis. He did admit to one-pack-per-day smoking, but had recently quitted.

Physical examination on admission revealed a chronically ill elderly male patient who was alert and oriented. Vital signs were: BP 120/70, PR 76/min-regular, BT 36.5oc. There was no icterus. Abdominal examination revealed an enlarged, firm, blunt-edged liver about 3 fingerbreaths below the right costal margin. Rectal examination was unremarkable.

Admission laboratory data showed: blood group AB, Rh positive, Hb 10.1 g/dl, white blood count 7,200/mm3, with neutrophil 71% eosinophil 6% and lymphocyte 22%, FBS 79 mg/dl, BUN 11 mg/dl, serum creatinine 0.6 mg/dl, Serum sodium 138 mEg/l, potassium 4.1 mEg/l, chloride 102 mEg/l, CO2 content 29 mEg/l, total bilirubin 1.1 mg/dl, direct bilirubin 0.5 mg/dl, alkaline phosphatase 101.5 U/l, SGOT 146 U/l, SGPT 75 U/l, serum albumin 2.95 g/dl, globulin 3.4 g/dl, prothrombin time 12.0 sec (control 11.4 sec), HBsAg positive, alphafeto protein positive, carcino-embryonic antigen 4.5 ng/ml, urinalysis was within normal limits and stool examination was positive for hookworm ova.

Further investigation revealed a normal chest x-ray and a normal barium enema. Ultrasonography of the hepatobiliary system confirmed an enlarged liver, with a large irregular mass occupying almost the entire right lobe. The portal vein was well-visualized. Subsequent CT-scan of the liver confirmed the presence of an infiltrative mass lesion with inhomogenous density involving the entire right lobe of the liver, compressing the inferior vena cava (Fig. 1). Portal vein involvement was suspected. Nuclear medicine scan of the skeletal system revealed no metastatic lesion. Celiac and superior mesenteric angiography also confirmed the presence of the large hepatic mass with normal hepatic arterial anatomy and a patent portal vein.

A diagnosis of primary hepatocellular carcinoma of the liver was entertained. Initial consideration of performing a hepatic resection was discouraged by

the size of the mass, which would have required an extended right hepatic lobectomy in order to completely remove the lesion. The close vicinity of the mass to the inferior vena cava would also have made such an attempt extremely risky and probably impossible. Furthermore, his HBsAg seropositivity and a likely cirrhotic liver would have made postoperative recovery with the rest of his left lobe very questionable at best. Since the tumor was still localized in the liver without any discernible evidence of extrahepatic metastasis, the option of performing an orthotopic liver transplant was offered to him. The nature and risk of the operation was thoroughly explained to him and his relatives. And after careful consideration he accepted the offer and was put on the transplant candidate list.

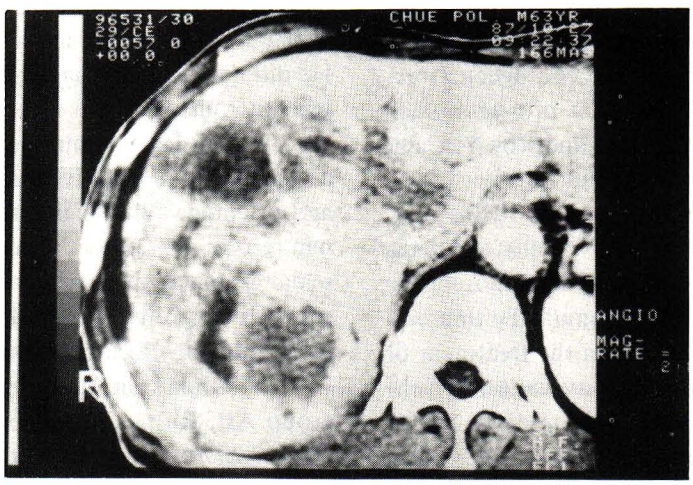

Figure 1 CT-scan of the liver demonstrated the presence of an infiltrative mass lesion with inhomogenous density involving the entire right lobe of the liver, compressing the inferior vena cava.

An urgent search was carried out to find a cadaveric donor. And on November 28, 1987, an unfortunate 43-year-old diabetic male patient was pronounced brain-dead at Chulalongkorn Hospital, 48 hours, after a futile operative attempt to evacuate a cerebellar hematoma. His family was approached and eventually consented to donating his internal organs for transplantation. His blood group was B, Rh positive.

The donor liver was subsequently harvested using the technic of in-situ perfusion, together with his heart and kidneys,[9] and then cold-preserved with Collin's solution. The operation on the recipient began with a thorough exploratory laparotomy through a bilateral subcostal incision with upper midline extension, which revealed no extrahepatic metastasis. A huge lobulated tumor occupied the entire right lobe and the medial segment of the left lobe, with the rest of the liver being cirrhotic. Recipient total hepatectomy was carried out with some difficulty due to its size. (Fig. 2)

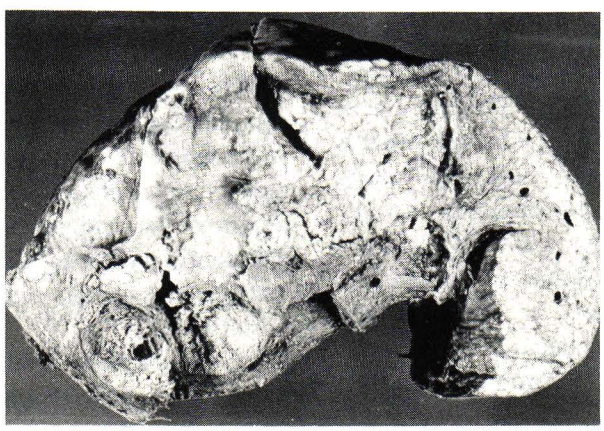

Figure 2 Showing a large hepatocellular carcinoma involving the cirrhotic liver.

After removal of the native liver, it was replaced with the harvested donor liver in an orthotopic fashion. Revascularization was then commenced with the suprahepatic caval anastomosis followed by the portal venous anastomosis. About 600 ml of lactated Ringer's solution at room temperature was flushed via the portal vein prior to the completion of its anastomosis, after which portal circulation was started, allowing the first 200 ml to escape through the donor infrahepatic vena cava. The suprahepatic caval control was then released. The infrahepatic caval and hepatic arterial anastomosis were then respectively completed. Satisfactory bile flow from the cut end of the grafted common bile duct was noted, after which the choledochojejunostomy anastomosis was then completed in a Roux-en-Y fashion.

Total warm ischemic time was about four minutes and cold ischemic time about three hours. Operative time was 5 hours. Estimated blood loss was 1200 ml. Four units of whole blood and four units of fresh frozen plasma, together with 1,800 ml of crystalloid solution were given during the operation. Three mg/kg of intravenous cyclosporine and 1 g of hydrocortisone were also given at the time of hepatic revascularization.

Postoperative immunosuppressive regimens consisted of intravenous cyclosporine 6 mg/kg/day in two divided doses and a tapering dosage schedule of methyprednisolone starting at 200 mg/day, and decreasing by a 40-mg decrement daily until a maintenance dose of 20 mg/day was reached. Recovery was satisfactory with signs of immediate hepatic function, as evidenced by an average prothrombin time of 17-18 sec (control 10.9 sec) during the first few postoperative day, and eventually lowered to about 11-12 sec by the fourth postoperative day.

Blood cyclosporine level was monitored weekly, with adjustment in the cyclosporine dosage aiming initially to keep a level of 800-1000 ng/ml. This eventually proved to be too high, as serum creatinine gradually rose to maximum level of 2.4 mg/dl on the eighteenth postoperative day. Another sign of cyclosporine toxicity was also encountered when he developed a grand-mal seizure on the tenth postoperative day, at which time cyclosporine level peaked at 922 ng/ml. Cyclosporine dosage was therefore lowered, and at the same time a starting dose of 0.5 mg/kg of azathioprine was added to the immunosuppressive regimens.

Pathological examination of the removed native liver showed a cirrhotic liver containing a 15 × 12 × 10-cm hepatocellular carcinoma occupying the entire right lobe and the medial segment of the left lobe (Figs. 2 & 3). A needle biopsy of the liver allograft performed at the time of surgery revealed mild fatty metamorphosis in the graft. Subsequently, percutaneous liver biopsy on the ninth postoperative day showed intrahepatic cholestasis with nonspecific change compatible with sepsis rather than rejection, at which time, a mild right upper quadrant localized peritonitis due a pseudomonas-contaminated subhepatic drainage catheter was discovered. This promptly recovered after catheter removal and administration of appropriate antibiotics.

A mild rejection episode with increased liver enzymes one week later, readily responded to two daily pulse doses of one and 0.5 g, followed by another tapering dosage schedule of oral prednisone.

He was finally discharged on the 33rd postoperative day on an immunosuppressive regimens consisting of 7.5 mg/kg/day of oral cyclosporine, 10 mg/day of prednisone and 1.8 mg/kg/day of azathioprine. Antihypertensive drugs were also necessary to control a recently developed hypertension, presumably due to the effect of cyclosporine. Liver function was satisfactory with a serum albumin of 3.75 g/dl, normal prothrombin time, and essentially normal liver enzymes, however, with a slight persistent elevation of serum bilirubin level at 2.5 mg/dl. HBsAg became negative immediately after surgery and remained negative at the last followup, while alpha-feto protein level was still positive on the eighteenth postoperative day, but eventually turned negative at the last follow-up 6 weeks after surgery.

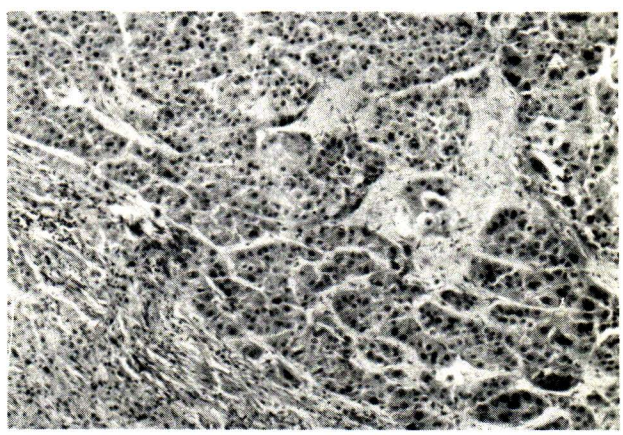

Figure 3 Trabecular pattern of hepatocellular carcinoma (H&E × 100).

DISCUSSION

In 1985, Iwatsuki et al. reported on the role of liver transplantation in the treatment of primary

hepatobiliary malignancies. In their subgroup of patients whose malignancies were not incidental findings, they reported a one-year survival rate of 30% if treated by azathioprine, prednisone and antilymphocyte globulin, and 68% if treated by cyclosporine and prednisone. However, those with primary hepatocellular carcinoma eventually died of recurrent disease after adequate long-term follow-up, except for those with the infrequent fibrolamellar type which carried a better prognosis. Suffice it to say that curative intent is absolutely unrealistic even with such a radical resection as performing a total hepatectomy and orthotopic liver transplant for such an extensive disease process. This, however, can also be said of any other therapeutic modality in treating the disease. What one can only hope for is a better quality of prolonged survival once the patient survives the operation.

Gordon et al. reported significant advantage of ABO blood group matching between donors and recipients.[11] Their reported first-time liver allograft failure rate were 40.0%, 58.3% and 61.5% respectively for ABO identical, ABO compatible and ABO incompatible matching combinations. We would also have preferred perfect ABO matching. But frequently, with the limited donor supply and the urgency of a recipient candidate in need of a new liver, a less-than-ideal match has to be accepted, which was the situation in the case reported.

Justification for widely employing the operation for this particular circumstance, taking into consideration the prohibitive expenses and efforts required, remains to be resolved. Any possible improved result combining liver transplant with other forms of systemic therapy, such as chemotherapy or immunotherapy also remain neither clear nor foreseeable with the current knowledge. The expedition carried out in this first reported case was certainly not with any intention to introduce a new heroic effort to treat such an extensive disease, but hopefully to signify the beginning of a new period of transplant surgery in Thailand. By proving the feasibility of performing a successful liver transplant with this experience, hopefully the procedure will find a more welcoming role the treatment of non-malignant endstage liver diseases, wherein a better purpose will be served.

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