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Small bowel transplantation using grafts from living-related donors. Two case reports

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Abstract A living-related small bowel transplantation (SBT) was performed in two pediatric patients with short bowel syndrome. In both cases, the donor was the patient's mother. The distal ileum (100 cm, 120 cm) was harvested and the ileocolic vessels, ileocecal valve, and terminal ileum were left intact. The two donors were discharged from the hospital on postoperative days 15 and 6, respectively. Recipient 1 was a 2 year 6 month-old boy with short bowel syndrome who underwent SBT due to loss of venous access. The graft vein was anastomosed to the recipient's infrarenal inferior vena cava. Despite triple immunosuppression (tacrolimus, steroid, and azathioprine), there were four episodes of rejection. The patient had been on total parenteral nutrition for almost his entire post-transplant course. He died from *Pneumocystis carinii* pneumonia 16 months after the transplantation. Recipient 2 was a 4 year 5 month-old girl with short bowel syndrome who underwent an isolated small bowel transplantation because of recurrent line sepsis. Her pretransplant bilirubin was 8.0 mg/dl and a biopsy showed severe fibrosis. The graft vein was anastomosed to the recipient's inferior mesenteric vein. After transplantation, her bilirubin level became normal within 10 days. Triple immunosuppression (tacrolimus, steroid, and cyclophosphamide) together with a 3-day course of OKT-3 made her post-transplant course feasible. After overcoming a single episode of rejection she left the hospital 4 months after SBT. The patient is currently (10 months after transplantation) hospitalized due to rejection, which is being successfully controlled, and she is off total parenteral nutrition. From our experience, harvesting of the distal ileum for use as a bowel graft can be safely performed. The advantages of living-related grafts, optimal graft length, and choice of vascular reconstruction in SBT are yet to be explored.

Key words Small bowel transplantation · Small intestinal transplantation · Living donor · Short bowel syndrome · Portal drainage · Liver dysfunction · Pediatric patient

Introduction

Small bowel transplantation (SBT) has been used clinically since the 1960s, but the initial results were unacceptable [1, 21]. Todo reported successful SBTs with the introduction of tacrolimus, which made SBT an effective strategy for the treatment of intestinal failure [3, 33].

Nevertheless, organ shortage has been a problem with cadaveric transplantation and in some countries,

including Japan, a cadaveric donor is unavailable due to religious and/or social backgrounds [11].

It is widely known and accepted that a partial resection of the intestine can be performed safely without affecting the patient's quality of life [13]. Moreover, adult patients can survive even after a massive resection of the small bowel, as long as the length of the remaining intestine exceeds 60 cm [17].

Taking these facts into account, the concept of living-donor SBT has emerged and a couple of trials have been documented [6, 7, 14, 16, 28, 29, 34]. This report describes our experience with two cases of SBT using living donors.

Case reports

Patient 1

The pre- and post-transplant course of patient 1 has been reported previously [10, 34]. Briefly, the donor was the recipient's 31-year-old mother (161 cm, 59 kg). The distal 100 cm of the ileum was resected out of her total small intestine length of 460 cm, leaving the terminal ileum intact. She was discharged on postoperative day 15 and has had no operation-related problems, including her nutritional status.

The recipient was a 2 year 6 month-old boy [12.9 kg (–0.1 SD) and 82.8 cm (–1.9 SD)] with short bowel syndrome due to a midgut volvulus at birth. He underwent SBT with a central line through the middle sacral vein after having lost all of his conventional venous access. A liver biopsy showed a fatty liver of mild grade. The blood type combination was identical (A to A) and the CDC test was negative. However, the donor and recipient were mis-matched on the three HLA loci (donor A 1,24; B 37,51; DR 9,10; recipient A 1,2; B 37,52; DR 10,15).

At operation, the length of recipient jejunum together with the duodenum was found to be 30 cm. The graft artery was anastomosed to the infrarenal aorta and the graft vein was anastomosed to the infrarenal inferior vena cava (IVC), both of them end-to-side. An ileostomy was made at the distal end of the graft and the abdomen could be closed without prosthesis. Immunosuppression consisted of tacrolimus, steroid, and azathioprine. The recipient met severe rejection on postoperative day 10, which was treated successfully with steroid pulse therapy. Thereafter three episodes of rejection followed, which caused the graft function to deteriorate. He had been on total parenteral nutrition (TPN) almost his entire post-transplant course. The patient died from *Pneumocystis carinii* pneumonia 16 months after transplantation.

Patient 2

Donor

The donor was the recipient's 31-year-old mother (174 cm, 52 kg). Blood type combination was identical (0 to 0) and CDC test was negative. The donor and recipient were mis-matched on three HLA loci (donor A 1,26; B 35,37; DR 12,13; recipient A 11,1,26; B 35,54; DR 8,12). She had no past medical history except for a Cesarian section. Her laboratory examination results were all normal. For both CMV and EBV, IgG Ab was positive. Based on the findings of preoperative mesenteric angiography, we planned to harvest the graft as shown in Fig. 1. During the operation, the mesenteric vessels were easily identified by transillumination. After dissection and systemic heparinization, the distal 120 cm of the ileum was resected out of her small intestine length of 580 cm, leaving the ileocolic vessels, ileocecal valve, and terminal ileum intact. On the backtable, the segmental graft was perfused with 217 ml of cold lactated Ringer's solution and then with 125 ml of University of Wisconsin (UW) solution. She was discharged from the hospital on postoperative day 6 and has had no nutritional status problems since that time.

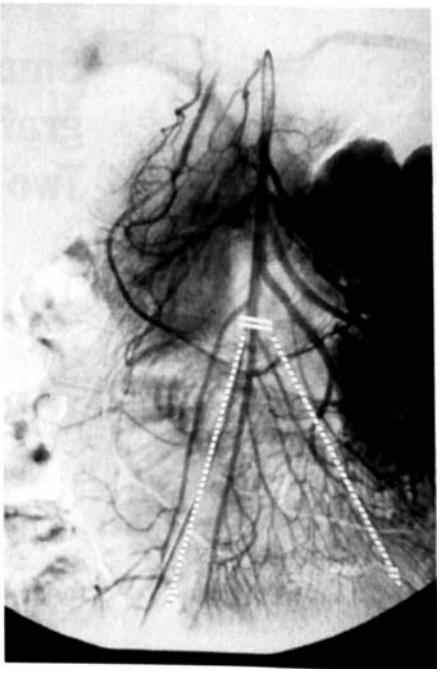

Fig. 1 Superior mesenteric angiography of the donor. The *broken line* shows the estimated resection line. Ileo-colic vessels were left intact to preserve the ileo-cecal valve and terminal ileum

Recipient's pretransplant course

The recipient was a 4 year 5 month-old girl who had been suffering from intestinal failure secondary to gastroschisis and intestinal atresia. As a result, she had been on TPN since birth. Before transplantation, she experienced a temporarily successful home TPN course, but frequent line sepsis had necessitated hospitalization and had caused obliteration of the vessels. At the time of SBT, only her right internal jugular vein remained intact, through which a catheter was inserted. Consequently, she was severely retarded both mentally and physically. Her height was 70.5 cm (–8.0 SD) and her weight was 6.1 kg (–5.0 SD). Her remaining duodenum and jejunum was estimated to be 25 cm by a pretransplant upper GI series. CMV IgG Ab and EBV IgG Ab were both positive. A lymphocyte crossmatch test between the donor and recipient was positive. Other pretransplant problems included hyperbilirubinemia and obliteration of the infrarenal IVC (Fig. 2). Her serum total bilirubin level had begun to rise 1 month before SBT and had reached 8 mg/dl at the time of the operation. An intraoperative liver biopsy showed severe fibrosis, but not cirrhosis. No splenomegaly was observed. Pretransplant angiography showed patent su-

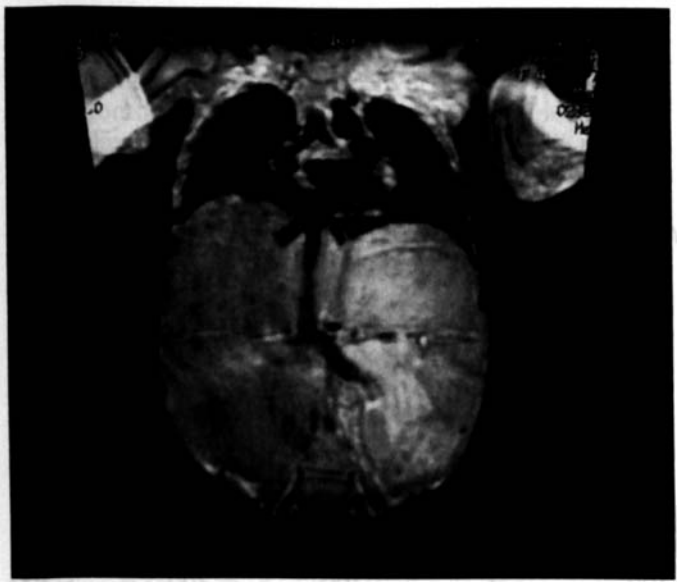

Fig. 2 Pretransplant MRI of case 2. Recipient's IVC was obliterated just distal to the renal veins

perior and inferior mesenteric veins, but the IVC was obliterated just distal to the renal veins.

Operation (Fig. 3)

At transplant, the graft artery was anastomosed to the infrarenal aorta in an end-to-side fashion with 7-0 Maxon interrupted stitches. The graft vein (6 mm in diameter) was anastomosed to the recipient's inferior mesenteric vein in an end-to-end fashion with 7-0 Maxon interrupted stitches. The UW solution was washed out with the recipient's blood through the venous anastomotic site just before completion of the venous anastomosis. The cold and warm ischemic times were 160 min and 74 min, respectively. Since tapering of the distended native intestine allowed the space for the graft, no technique such as skin closure or closure with mesh was necessary.

Post-transplant management (Fig. 4)

Post-transplant immunosuppression consisted of tacrolimus, steroid, and cyclophosphamide, as well as a 3-day course of OKT3. Her total bilirubin level became normal within 10 days. The first episode of mild rejection was successfully controlled with steroid pulse therapy. She resumed tube feeding, and then oral intake of water and solid food on postoperative days 3, 5 and 10, respectively. The patient was discharged from the hospital 4 months after the transplant with feasible weight gain. Unfortunately, she returned 1 month later with severe rejection. Following that, and treatment for another rejection episode which occurred 8 months after transplantation, she is doing well without TPN. It was confirmed that her graft could be observed through retrograde fiberoptic endoscopy from the anus, so we are considering closing the stoma in the near future.

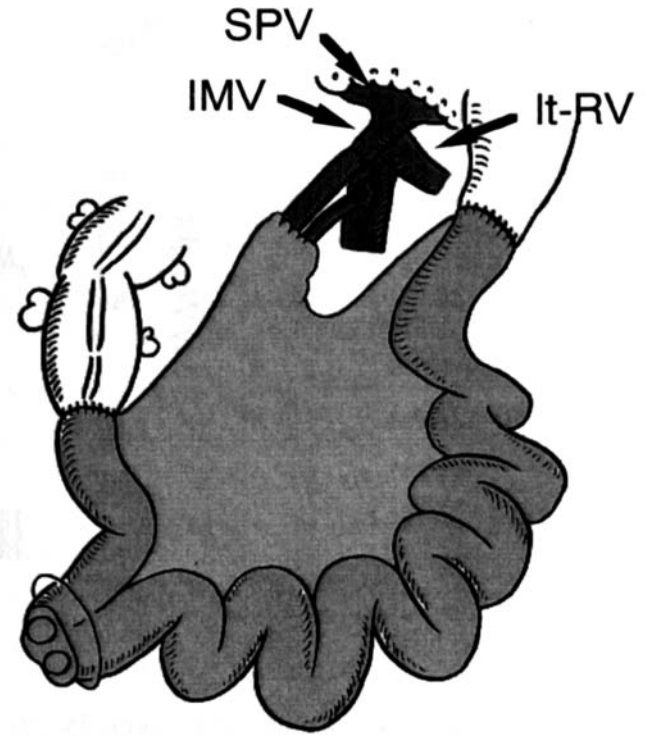

Fig. 3 Illustration of the graft implantation for case 2. The graft mesenteric vein was anastomosed to the recipient's inferior mesenteric vein. A loop ileostomy was made for the biopsies. *IMV*, inferior mesenteric vein. *Lt-RV*, left renal vein. *SPV*, splenic vein

Discussion

Rationales for living-related grafts

The reasons for using a living donor with SBT are safety during the donor operation, cadaveric graft shortages, a short ischemic time, and possible immunological benefit in the case of related donors.

A bowel resection for SBT donors is safe and the postoperative course is generally satisfactory, as reported in previous studies [6, 7, 14, 16, 28, 29, 34]. However, the terminal ileum as well as the ileocecal valve should be preserved to avoid weight loss and nutrient deficiency [14, 25].

The lack of suitable intestinal grafts due to, for example, the recipient's physique, can occur even in those countries where cadaveric transplantation is popular [14], and to a much greater extent in countries like Japan, where cadaveric donors are very scarce [11].

When considering ischemia time, the shorter the better is the generally accepted rule. Living donor grafts can achieve shorter ischemia times, which would then bypass another problem not yet elucidated, the optimal conditions for bowel graft preservation.

We expect an immunological advantage with living-related grafts. As is deducible from clinical kidney

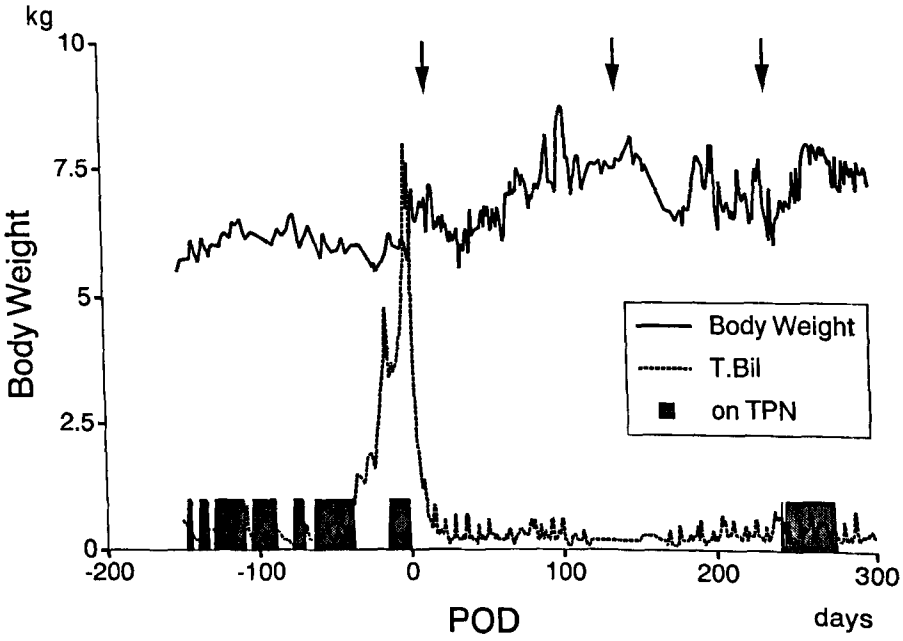

Fig. 4 Changes of body weight and total bilirubin level together with rejection episodes and duration of TPN in case 2. *POD*, postoperative date. *TPN*, total parenteral nutrition

transplantation, as well as canine SBT reports [5, 23], there may be an advantage to using haplotype-identical donors for clinical SBT as well. Recently, Benedetti et al. reported favorable results with a graft from an HLA-identical living related donor [29].

These factors may be the breakthrough we have been seeking in the current status of SBT, as the 3-year patient survival rate with an isolated small bowel graft remains at around 60% [12]. The present study results were not satisfactory in our limited experience. Our recipients with bowel grafts from living donors met rejection episodes as frequently as those with cadaveric, non-related grafts.

Problems with living related SBT

Graft length

One problem with grafts from living donors is that the length of the graft is limited. Gruessner et al. reported a successful living-related SBT for adult recipients with 200 cm ileal grafts [14]. Other promising reports have stated that 160 cm is enough for adult recipients, when using an isograft from an identical twin or triplet. This can provide physiological and functional control without immunological barrier effects [4]. We thought that a 100 cm graft would be sufficient for pediatric recipients, but the unsatisfactory body weight gain with our second case suggests that the graft length may have been insufficient.

Vascular reconstruction

Another problem for discussion is how to reconstruct the vessels, about which there have been many controversial studies. Kaneko et al. reported that systemic drainage is preferable from a technical feasibility viewpoint, and we adapted his method in our first case [18]. However, many reports support portal drainage from immunological [26] and metabolic [20, 30, 33] points of view. Still others have stated that there is no difference between these two methods of reconstruction regarding bacterial translocation [9] and the immunological [31], and metabolic [15] aspects. We introduced portal drainage reconstruction in our second case because of the lack of infrarenal IVC and because we expected recovery of the patient's liver dysfunction.

Liver dysfunction and timing for transplant: combined liver/bowel transplantation or isolated bowel transplantation

Patients with intestinal failure while on TPN are at high risk of developing liver dysfunction. The cause can be TPN itself [22], bacterial translocation [27], infection [8], fasting [24], manganese toxicity [19], or multifactorial [32]. If irreversible liver disease such as cirrhosis develops, then a simultaneous liver/bowel transplantation must be considered. There is no definite criterion for when to make the decision on which mode of operation, i.e., isolated bowel transplantation or combined liver and bowel transplantation, is to be

performed. Based on their experience, Beath et al. stated, "The natural history of TPN-associated liver disease is that of progressive liver failure and death 6–12 months after onset of cholestasis, defined as bilirubin level of greater than 100 μmol/l (5.88 mg/dl)" [2]. The total bilirubin level in our second case at the time of SBT was 136 μmol/l (8.00 mg/dl). Fortunately, the recipient's bilirubin level went down to within normal limits within 10 days. The preoperative findings which supported our operative mode selection, i.e. isolated bowel transplantation, were an absence of splenomegaly and short duration (2 days) of hyperbilirubinemia over 5.88 mg/dl. The intraoperative liver biopsy was also favorable, i.e., free from cirrhosis. We would consider a living-related combined liver/bowel transplantation for a future case of intestinal failure with liver cirrhosis.

Conclusion

Many more cases of SBT are required before the optimal selection of implanted graft type can be determined, to provide the necessary data for understanding the optimal vessel reconstruction mode, and to evaluate the advantages of living-related grafts.

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