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Identical Twin Small-bowel Transplantation Without Maintenance Immunosuppression: A 5-year Follow-up and Literature Review

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Background. The availability of an identical twin donor that allows avoidance of complications related to graft rejection and immunosuppression represents an ideal treatment option for irreversible intestinal failure. **Methods and Results.** We described a 45-year-old woman who lost most of her small bowel due to acute superior mesenteric thrombosis received a living-related small bowel transplant from her identical-twin sister. Monozygosity was established by buccal smear DNA amplification using short tandem repeat. A pretransplant panel-reactive antibody was 47.5% with several HLA antibodies in higher titers. The patient received a brief course of steroids without any additional immunosuppressive agents after transplantation. Her postoperative course was uneventful without an episode of rejection or infection. The preformed HLA antibodies steadily declined over time after transplantation. At a 5-year follow-up, the patient achieved full enteral autonomy from parenteral nutrition with a regular lifestyle. **Conclusions.** Identical-twin intestinal transplantation appears to provide the best outcomes by avoiding complications related to rejection and immunosuppression. We provide evidence that it may confer greater long-term immunological advantages even in a high-immunologic risk recipient.

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The intestine has the highest rate of rejection among commonly transplanted solid organs. Despite advances in surgical techniques over the past decade, rejection and associated infection are the most formidable barrier to successful intestinal transplantation (ITx).[1,2] Current actuarial patient survival rates are 76%, 56%, and 43% at 1, 5, 10 years, respectively, well behind other solid-organ transplants. The presence of specialized lymphoid organs, the vast number of hematopoietic cells contained within the transplanted intestine and constant environmental exposures may be contributing factors to the high rate of rejection and infection.[3,4]

Transplants from HLA-identical siblings usually result in favorable long-term outcomes and transplants from identical twins represent the most favorable outcomes.[5] Perfect haploidentity has potentially enabled these individuals to be transplanted without the need for immunosuppressive medications and the associated adverse effects.[6] Identical intestinal transplants (IdITx) are extremely rare. Up to date, only 4 cases have been reported in the English literature (Table 1)[7-10] and account for approximately 0.17% of all intestinal transplants worldwide.[1]

In this report, we describe a high immunologic risk recipient who underwent a living donor intestinal transplant from her monozygotic twin sister. Her postoperative course was uneventful without the use of immunosuppressive agents. At a 5-year follow-up, the patient showed no evidence of rejection and achieved full enteral autonomy from parenteral nutrition.

CASE REPORT

In May 2013, a 45-year-old female was referred to our institution for short bowel syndrome secondary to acute superior mesenteric thrombosis. Four months earlier, she underwent a right hemicolectomy plus massive small bowel resection except the proximal 15 cm of jejunum and had been on total parenteral nutrition (TPN) since then. She was soon considered as a bowel transplant candidate both because of

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TABLE 1.

Summary of worldwide identical twin intestinal transplants

Case	Year/place	Age	Sex	Diagnosis	I/S	Outcomes/follow-up
1	1995/Stanford California (USA)[7]	34	M	Desmoid tumor	None	Alive/TPN-free at 1 y
2	1997/Cambridge (UK)[8]	40	M	SMV thrombosis	None	Alive/TPN-free in 1997
3	2000/Geneva (Switzerland)[9]	13	M	Mid-gut volvulus	None	Alive/TPN-free at 5 y
4	2002/Chicago Illinois (USA)[10]	33	M	Churg-Strauss syndrome	Yes (prednisone)	Alive/TPN-free at 2.5 y
5	2013/Xi'an (China)	45	F	SMA thrombosis	None	Alive/TPN-free at 5 y

I/S, immunosuppression; SMV, the superior mesenteric vein; SMA, the superior mesenteric artery.

availability of her twin sister and inability to obtain TPN in her hometown. The protocol regarding clinical intestinal transplantation was approved by our institutional review board and consistent with the Principles of the Declaration of Istanbul as outlined in the "Declaration of Istanbul on Organ Trafficking and Transplant Tourism". The donor's "B" blood type was the same as that of the recipient. HLA matching (A11, 24; B62, 48; Cw8, 9; DR9, 16; DQ5, 9) was identical between the 2 twins. Monozygosity was further established by buccal smear DNA PCR amplification using short tandem repeat (STR). Pretransplant peak panel-reactive antibody (PRA) of the recipient was 47.5%. The Luminex specificity testing identified both class I non-donor-specific antibody (DSA) to B27, B67, and B42 at levels of 2355, 1768, and 1344 mean fluorescent intensity and class II non-DSA to DR11, DR13, DR14, and DR8 at levels of 12 238, 12 196, 10 605, and 9206, respectively. The major histocompatibility complex class I chain-related gene A was detected at levels of 2350 mean fluorescent intensity. A direct complement-dependent cytotoxicity crossmatch testing was negative. Both the donor and the recipient were serologically cytomegalovirus (CMV) negative before the procedure. Both the donor and the recipient had the antibody to hepatitis B surface antigen, the antibody to hepatitis B core antigen, and the antibody to hepatitis B e-antigen.

The donor's distal 155-cm ileum was transplanted into the recipient by a previously described method.[11] The distal superior mesenteric artery and vein of the ileal graft was anastomosed in an end-to-side fashion to the recipient's aorta and inferior vena cava, respectively. The graft was anastomosed proximally to the recipient's remaining jejunum in a side-to-side fashion and distally to the stump of the transverse colon in an end-to-side fashion. An end ileostomy 10 cm proximal to the side-to-end ileocolostomy was performed to monitor graft function and to allow easy access for endoscopic surveillance and biopsy. Total operative time was 6.0 hours in the recipient and 2.2 hours in the donor. Cold ischemia time was 77 minutes with a warm ischemic time of 2 minutes. Estimated blood loss in the recipient was 300 mL with no requirement for blood transfusion.

The patient received intravenously methylprednisolone at a dose of 500 mg 1 day before and 2 days after transplantation for reducing an ischemic-reperfusion injury, and no immunosuppressive agents were additionally administered afterward. She had an uneventful postoperative course. Intravenous heparin was initiated on postoperative day 1 to achieve and maintain an activated partial thromboplastin time of 1.5 to 2.0 times control. As a heparin drip was discontinued 5 days later, 100 mg of aspirin per day was started and continued for a year. The donor was discharged on the sixth postoperative day with an uneventful recovery.

The patient was completely off TPN and was on a normal diet on the 12th postoperative day. She did not need TPN or any supplemental parenteral nutrition or intravenous fluids thereafter. The ileostomy was reversed 3 months after transplantation. The patient had 4 to 6 bowel movements per day during the first month, which stabilized to 1 to 3 times per day 1 month after closure of the ostomy. Body weight loss was initially seen and has stabilized 12 months after the procedure. Low levels of serum prealbumin and retinol-binding protein were seen, and these values gradually normalized 3 months after ITx. The levels of serum cholesterol and triglycerides remained low during the first postoperative year and resumed a normal range 1 year later. Serum vitamin B12 and folic acid were in the normal range. Serum

TABLE 2.

Nutritional status, serum lipids, and vitamins after transplantation

Parameters	Time after transplantation, mo						
	0	3	6	12	24	36	48
Body weight, kg	41	40	37	42	43	43	44
Albumin, g/L	32	36	38	40	42	45	44
Prealbumin, g/L	0.11	0.24	0.25	0.26	0.31	0.28	0.32
Retinol-binding protein, mg/L	12.4	21.4	36.2	37.7	41.2	37.7	40.2
Cholesterol, mmol/L	4.6	2.3	2.8	3.2	4.2	4.3	4.2
Triglycerides, mmol/L	1.32	0.25	0.43	1.21	1.14	1.16	1.20
Vitamin B12, pmol/L	437	415	527	392	462	528	477
Folic acid, nmol/L	10.5	13.7	15.2	15.7	14.1	11.6	13.5
Vitamin D3, ng/mL	11.4	9.3	15.8	16.4	18.5	21.4	20.6

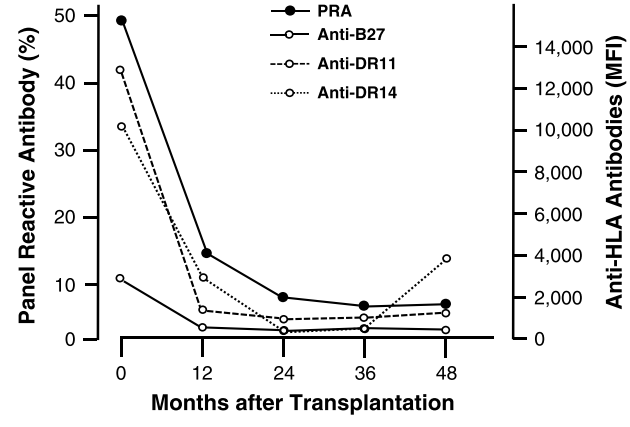

FIGURE 1. Evolution of serum PRA and HLA antibody levels after identical-twin intestinal transplantation. The levels of PRA and HLA antibodies gradually decreased over time.

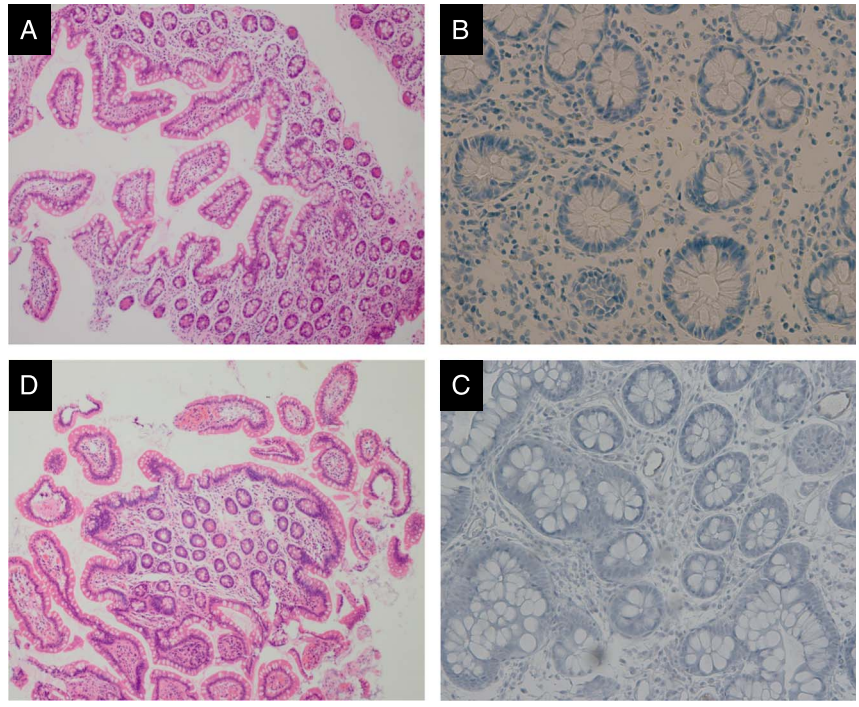

FIGURE 2. Histopatholgy of the intestinal allograft. A and B showing normal mucosal architecture of small bowel biopsies with no staining for C4d in the capillaries of the lamina propria 4 days after transplantation. C and D showing no evidence of villous atrophy, submucosal fibrosis, and C4d deposition in the submucosal capillaries and small vessels 4 years later.

vitamin D3 remained low despite oral supplementation postoperatively (Table 2).

Histology showed normal mucosal architecture with no C4d deposition in the submucosal capillaries and small vessels at the time of early transplantation and 4-year follow-up biopsy with no evidence of antibody-mediated graft injury (Figure 1). The levels of PRA gradually declined and were below 10% 4 years later. The HLA antibodies steadily declined over time after transplantation, and no DSA was detected. At a 5-year follow-up, both class I and class II antibodies remained low (Figure 2 and Table 3). The recipient's CMV and Epstein Barr virus PCR results remained negative during the study period.

The donor had an uneventful recovery and was discharged home on postoperative day 4, tolerating a general diet and resuming normal activities. She had mild diarrhea (3 to 5 stools per day) in the first month, which decreased to 2 to 3 times per day by the second month after the procedure. Episodes of diarrhea were easily controlled with diet modifications without any antidiarrhea medications. Her serum cholesterol and triglyceride levels were always in the normal range after donation.

DISCUSSION

In the present case report, we describe the clinical course of a patient who underwent a living donor identical-twin intestinal transplant with excellent long-term graft function. The recipient had never developed rejection without immunosuppressive medications except a brief course of steroids postoperatively. At a time of 5-year follow-up, the patient achieved enteral autonomy from TPN with a good nutritional state. We provide evidence that an identical-twin intestinal transplant confers the greater immunological advantage that permits avoidance of immunosuppression and its associated adverse effects in case of major intestinal failure and TPN-related complications.

Total parenteral nutrition currently remains the first-line treatment for short-gut syndrome in China. Intestinal transplantation is usually considered as treatment of choice for patients who develop intractable TPN-related complications including liver dysfunction, lack of central venous access, and catheter-related sepsis. Because of scarce source of cadaveric donation in our country, living-related ITx remains the major form of ITx. Our short and midterm outcomes have steadily improved over the last few years. In 10 patients undergoing living-related ITx in 2010 to 2015, graft survival at 1

TABLE 3.

Evolution of anti-HLA antibodies after transplantation

		Time after transplantation, mo				
	HLA types	0	12	24	36	48
Class I	B27	2354.7	584.5	435.6	521.4	443.2
	B67	1768.4	347.9	431.4	511.8	729.7
	A80	ND	ND	ND	ND	1346.4
	Cw17	ND	ND	ND	ND	1231.9
Class II	DR11	12238.0	1945.4	1251.2	1323.3	1342.8
	DR13	12195.6	3315.2	2105.1	1017.4	858.9
	DR14	10604.9	3553.5	514.7	619.9	3916.4
	DR8	9206.3	2905.4	654.2	1532.8	3274.7
	DR9	ND	ND	ND	ND	2362.3
	DQ4	ND	ND	ND	ND	1556.4
	DR52	ND	ND	ND	ND	4122.6
MICA	MICA02	2349.9	1334.4	ND	ND	ND
	MICA17	923.7	521.8	ND	ND	ND

ND, nondetected; MICA, major histocompatibility complex class I chain-related gene A.

and 3 years is 90% and 80% in our institution, respectively. Therefore, ITx is now offered to patients who have inability to obtain long-term TPN and those who have a very poor quality of life on TPN or have a well-matched donor even in the absence of complications.

In identical-twin transplant recipients, the requirement and degree of immunosuppressive agents remains uncertain.[12-14] Increasing evidence has shown that monozygous twins can and do differ genetically in response to the environment and aging, with changes mainly affecting single base pairs, and rarely at large genomic regions.[6,15] Whether such minor differences are capable of triggering allograft rejection between identical twins remains unknown. Based on limited data available from renal identical-twin transplants, risks of rejection appear to be low with excellent long-term outcomes. In response to the surgical trauma and the subsequent ischemia-reperfusion damage to transplanted organs, innate immune responses are initially activated, irrespective of complete HLA homology between the donor and recipient. The use of short-course of steroids in the postoperative period may block innate immune responses and their correlation to adaptive alloreactivity at various levels and potentially reduce risk of acute rejection.[13] In renal transplantation, primary disease recurrence is one of the major common causes for graft loss and some authors recommend keeping maintenance immunosuppression to prevent disease recurrence. In previous 4 identical intestinal transplants, 3 did not receive any immunosuppression and 1 was initially given cyclophosphamide and maintained on chronic steroids to prevent recurrence disease. Although available evidence to guide immunosuppression use in IdITx is extremely limited, we suggest that a prudent approach should be individualized based on the risk of primary disease recurrence, immunological risk status, history of previous transplantation, and so on.

One of our major concerns for this case was the possible development of humoral rejection due to the high levels of pretransplant HLA antibodies. There was a case report in the literature describing acute humoral rejection in HLA-identical sibling renal transplantation under a calcineurin inhibitor.[16] An isolated small bowel transplant appears to render the graft more susceptible to antibody-mediated immune damage compared with a liver-inclusive transplant. Our previous publications showed that the incidence of chronic rejection is as high as 15% to 20% 3 to 4 years after ITx.[17] In previous 4 cases of IdITx, there were no evidence of chronic rejection at a 1, 1, 2.5, 5 years after IdITx. In our particular case, we closely followed the evolution of preexisting and possible newly formed HLA antibodies and showed steadily decreased levels of preexisting HLA antibodies without newly formed antibodies. At a 5-year follow-up, the patient had a well-functioning transplant with no histologic evidence of graft damage, suggesting that immunosuppressants may not be necessary to avoid chronic rejection in IdITx recipients.

Nutritional outcomes after living-related ITx remain largely unknown. We and others have shown that 160 to 180 cm of a segmental bowel autograft or allograft from a living donor is capable of supporting the minimal nutritional requirements in adults.[18] Previous reports indicated that complete disruption of the lymphatic drainage of the graft may affect fatty acid absorption after IATx.[19] Indeed, the ongoing low levels of serum cholesterol and triglycerides in our case may be a reflection of fat malabsorption caused by disruption of the graft lymphatic drainage.[20,21] Similar to our findings, several studies previously showed that fat malabsorption was common after cadaveric-donor ITx, as reflected by steatorrhea and low serum cholesterol levels.[22,23] Fecal fatty acids were not assessed in our study due to the unavailability of this technique in our center. Low triglyceride levels have not been previously reported after ITx. Compared with cadaveric-donor ITx, shorter absorption length in a live-donor graft may contribute to low serum triglyceride levels. In addition, ITx recipients may be more susceptible to vitamin D deficiency due to fat malabsorption, and vitamin D supplementation may be beneficial for decreasing bone loss after ITx. In our single case, the length of the transplanted intestinal allograft is 155 cm, and the patient has not required TPN or any supplemental parenteral nutrition or intravenous fluids after hospital discharge.

In conclusion, this case and other small series case reports indicate that IdITx appear to be the best treatment option for patients with intestinal failure and TPN-related complications. We provide evidence that IdITx confer a greater long-term immunological advantage even in a high immunologic risk recipient.

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