CASE 8

An Isolated Complete Intestinal Transplantation in an Adult: A Complicated Postoperative Course

Case presentation:
KAREEM M. ABU-ELMAGD, SATORU TODO, ANDREAS TZAKIS, KENJIRO NAKAMURA, HARLAN WRIGHT, JOHN FUNG, JORGE REYES, ROBERT GORDON, DAVID H. VAN THIEL AND THOMAS E. STARZL
Pittsburgh

Commentary:
JAMES WILLIAMS
Chicago

A 31-year-old black male was referred to the University of Pittsburgh Medical Center five months after he lost his entire small bowel. (Fig. 1) The patient had multiple gun-shot injuries to the abdomen and was placed on total parenteral nutrition (TPN) after unsuccessful multiple attempts to reconstruct the main superior mesenteric vessels. Because continuity of the gastrointestinal tract was not restored at the time of surgery, induced vomiting was the only way to drain the gastroduodenal and biliary secretions. At the time of initial evaluation, the biochemical liver function tests were good and the patient was accepted as a candidate for an isolated small intestinal transplantation (SBTx).

Donor Information. On May 2, 1990, a suitable donor became available and the whole small bowel was transplanted. The donor was young (36 years old), Caucasian, of the opposite sex and smaller in size compared to the recipient. The graft was ABO identical (O +ve), HLA incompatible and the cytotoxic cross match was negative. Selective decontamination of the donor's gut was attempted utilizing Amphotericin B, gentamycin and polymyxin E with no efforts to alter the graft lymphoreticular tissue with either OKT3, ALG or other modalities. The whole small bowel was harvested by Dr. Starzl and was preserved by simple immersion in an ice bath without vascular flushing. The intestinal lumen was irrigated with cold lactated Ringer's solution, and the graft was preserved for 10.5 hours.

Recipient Operation. Extensive adhesions were evident at the time of surgery because of the previous multiple abdominal operations. The gallbladder was injured during kocherization of the duodenal stump and dissection of the transverse colon which necessitated cholecystectomy. The technique of the graft implantation was similar to that originally used by Lillehei in dogs more than 30 years ago, except that arterialization was with a free segment of the recipient internal iliac artery that was interposed between the superior mesenteric artery (SMA) of the graft and the recipient infrarenal aorta. (Fig. 2) After tedious dissection, the distal stump of the recipient superior mesenteric vein (SMV) was found and anastomosed to the graft SMV using a segment of the donor iliac vein as an interposition graft. The proximal segment of the graft jejunum was anastomosed side-to-side to the recipient duodenal stump, and the intestinal graft was vented at both ends by a chimney-type proximal jejunostomy and distal ileostomy. Both vents allowed closed monitoring of the graft and adequate early decompression of the GI tract. Continuity of the alimentary canal was completely restored in two stages. The proximal jejunal stoma was first closed 8 weeks after transplant and the terminal vent was then excised at 16 weeks with construction of a side-to-side ileocolic anastomosis.

Postoperative Management. The basic immunosuppressive therapy was FK 506. The drug was initially given intravenously twice per day with a total dose of 0.15 mg/kg (infused over 4 hours). Enteral administration was started on postoperative day (POD) 18 with a beginning dose of 0.3 mg/kg/day. (Fig. 3) Dose adjustments and discontinuance of intravenous FK 506 therapy were made based upon the quality of intestinal graft function, daily FK 506 trough plasma levels, oral FK 506 pharmacokinetic studies, evidence of graft rejection and development of renal

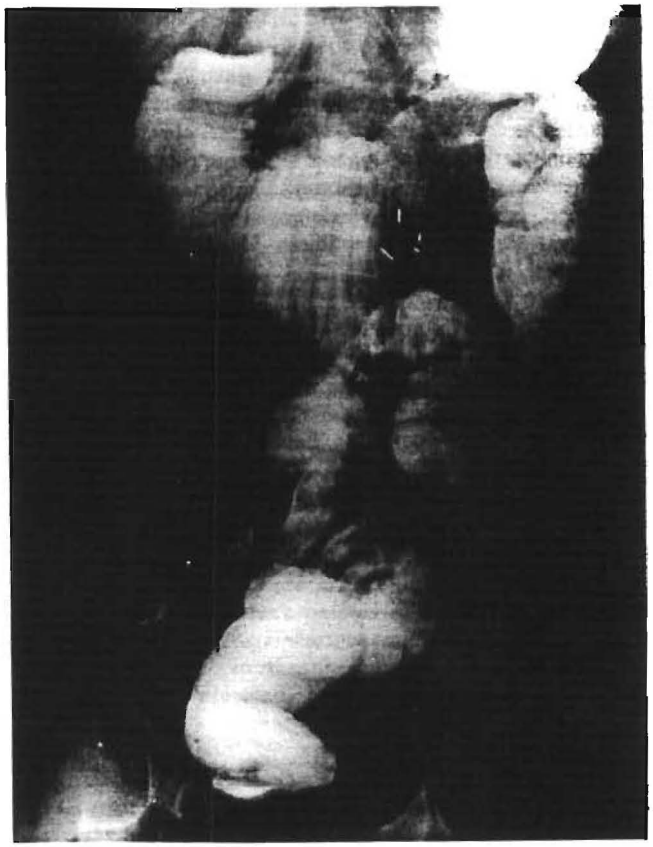


Figure 1: GI series and barium enema before small bowel transplantation. The residual GI tract consisted of the stomach, the duodenal loop that ended blindly and the left colon.

Correspondence: Thomas E. Starzl, M.D.; Univ. of Pittsburgh Medical School; 3601 Fifth Ave.; Pittsburgh, PA 15213. James Williams, M.D.; Rush-Presbyterian-St. Luke Hospital: 1653 W. Congress Pkwy.; Chicago, IL 60612.

dysfunction. Maintenance steroid therapy was started on POD 14 with an initial dose of 30 mg/day which was gradually reduced to 10 mg. Fifteen months after transplantation a low dose of azathioprine (0.8 mg/kg/day) was added to the previous immunosuppressive regimen.

Intestinal decontamination was adopted for the first six postoperative weeks using a combination of Amphotericin B, gentamycin and polymyxin E on a four times daily regimen. The patient also received systemic ampicillin and Cefotaxime as prophylactic antibiotics during the first five postoperative days. With each rejection episode, selective decontamination was reinstituted for a period of one to two weeks and guided by frequent blood and quantitative stool cultures.

Monitoring of intestinal functions and detection of graft rejection was based primarily on clinical, histopathologic, endoscopic, radiologic, anthropometric and metabolic parameters.

Despite the stormy postoperative course with sluggish resumption of the gastrointestinal functions that required protracted initial hospitalization (five months) and repeated readmissions (six times), the patient is still alive 18 months after transplantation with satisfactory graft functions. The remarkable events that complicated the patient management and his postoperative care are the following:

Temporary Liver Dysfunction. Before transplantation, there was no biochemical evidence of significant liver dysfunction; normal serum bilirubin (0.7 mg/dL), serum albumin (3.4 g/dL) and prothrombin time (12.8 seconds). The liver enzymes were slightly elevated with a level of 72 IU/L (SGOT), 84 IU/L (SGPT), 103 IU/L (alkaline phosphatase) and 331 IU/L (δ-GTP). The liver biopsy at the time of surgery showed centrilobular steatosis with cholestasis, arteriolar thickening and hemosiderosis. On the third postoperative day, the total serum bilirubin increased to 4.4 mg/dL (direct: 2.9 mg/dL) with significant prolongation of the prothrombin time (17.6 seconds). There were no concomitant skin lesions suggestive of graft-versus-host disease and liver biopsy was not obtained. The operative requirement for blood transfusion was minimal, and the patient did not receive any anticoagulant therapy. Recovery was gradual, and all values returned to the normal range by the end of the second postoperative week.

Permanent Renal Failure. Kidney function was normal at the time of SBTx with BUN of 19 mg/dL and serum creatinine of 0.4 mg/dL. A significant reduction in urine output with a steady increase in both parameters was noticed during the first 10 postoperative days. On the 14th postoperative day hemodialysis was started due to severe renal insufficiency. (Fig. 3) At that time the patient had a severe rejection episode with intermittent hypotension and high FK 506 trough plasma levels and received a combination of different nephrotoxic antibiotics including amphotericin B. Renal ultrasound which was done periodically showed significant reduction in the size of both kidneys with no evidence of renal vascular occlusion. The patient is currently on hemodialysis awaiting kidney transplantation.

Graft Rejection. Recurrent episodes of intestinal graft rejection developed in both the early and late postoperative periods.

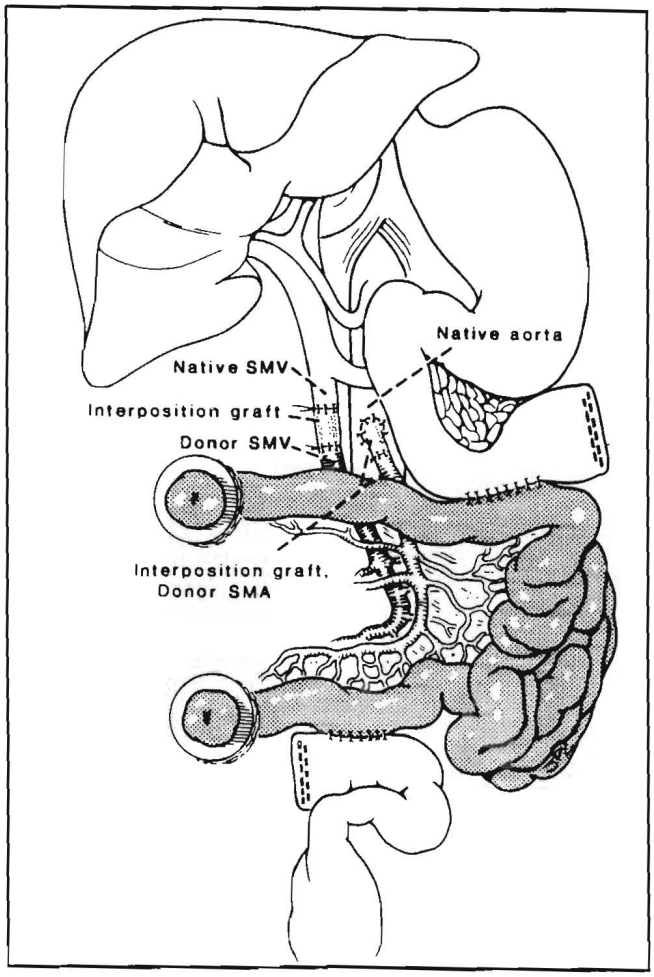
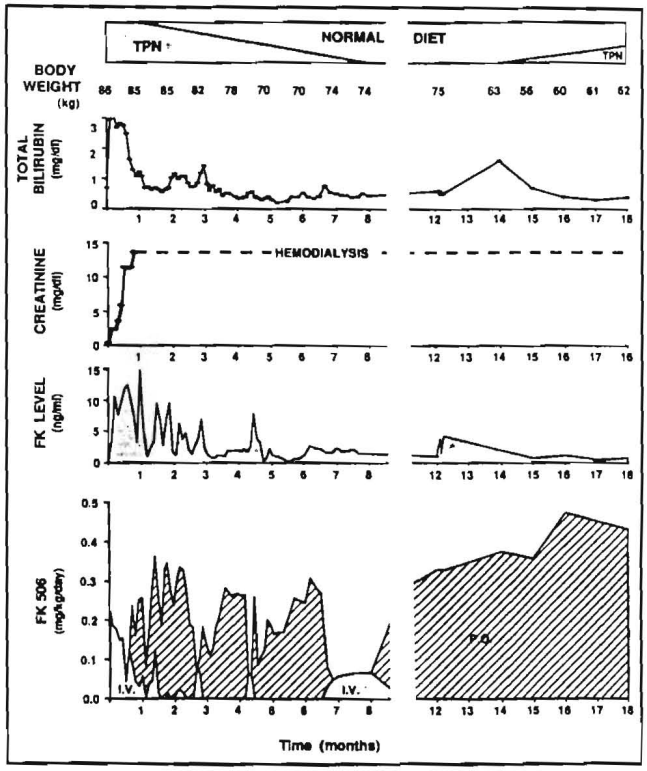


Figure 2 (left). The graft SMA and SMV are connected to the recipient infrarenal aorta and SMV, respectively, using interposition grafts. The two ends of the intestinal graft are exteriorized by chimney enterostomy at the upper and lower right quadrants of the abdomen.

Figure 3 (below). The postoperative clinical course with close monitoring of FK 506 doses, drug trough plasma levels, serum creatinine and total bilirubin.



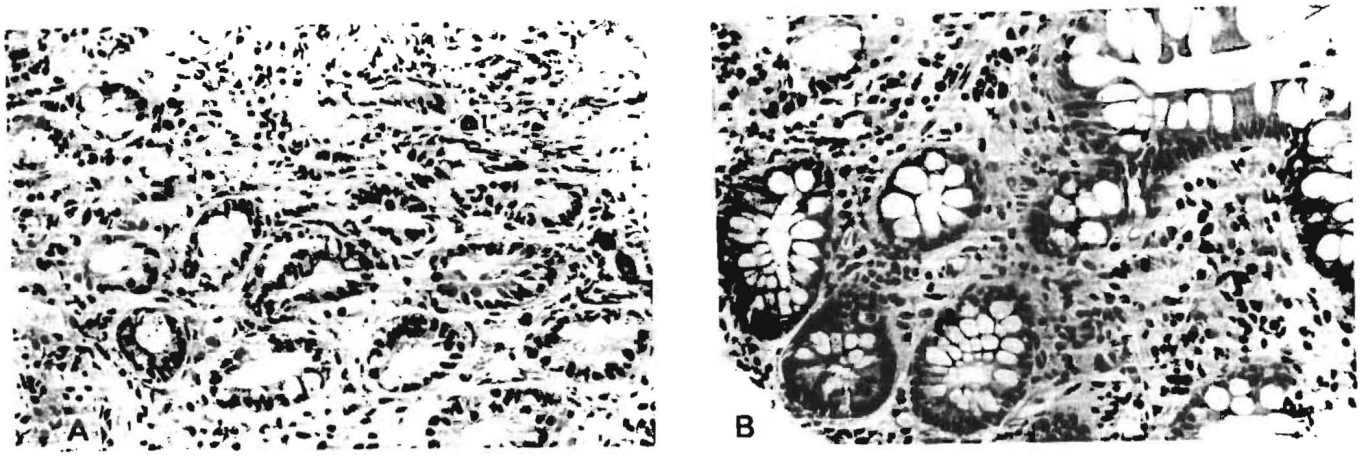


Figure 4: Histological monitoring of intestinal graft rejection. A) Prominent rejection with a mixed cellular infiltrate composed of activated lymphocytes and plasma cells. Epithelial damage of crypts and depletion of goblet cells are also evident (H&E, x480). B) Treated rejection with less cellular infiltrate and intact crypts with normal goblet and Paneth cells (H&E, x480).

(Table 1) The first endoscopic biopsy on POD 7 showed mild cellular infiltrates, cryptitis and villous edema. The patient was receiving FK 506 as the only immunosuppressive agent at that time and was running high drug plasma levels. On the evening of POD 14, the patient developed high fever (39° C), abdominal pain and high watery stomal output (> 3 L within 24 hours). On physical examination the abdomen was distended with infrequent bowel sounds and the mucosa of both the jejunal and ileal stomae was edematous and dusky in color. Emergent endoscopy showed edematous flat mucosa, diffuse hyperemia and multiple ulcerations particularly in the distal ileum. Multiple endoscopic biopsies were obtained and sent for histopathological examination. Meanwhile the patient started to develop mental confusion, hypotension and metabolic acidosis. Therefore treatment was initiated immediately with 2 gm Solumedrol and 10 cc of OKT3. In the next morning, the diagnosis was histologically documented (Fig. 4A), another 1 gm Solumedrol was given and the patient continued to receive OKT3 for a total of seven days. Also, maintenance steroid therapy was started with a daily dose of 30 mg. Recovery was clinically obvious within 24 hours. The endoscopic examination at the end of the OKT3 course revealed normal mucosal appearance and the obtained biopsies documented marked histological improvement. (Fig. 4B) On POD 37 there was clear clinical evidence of another rejection episode but with minimal histological changes. Two grams of Solumedrol were then given with an increase in FK 506 doses. The subsequent endoscopic protocol biopsies declared another two episodes of mild histological graft rejection during the rest of the first initial

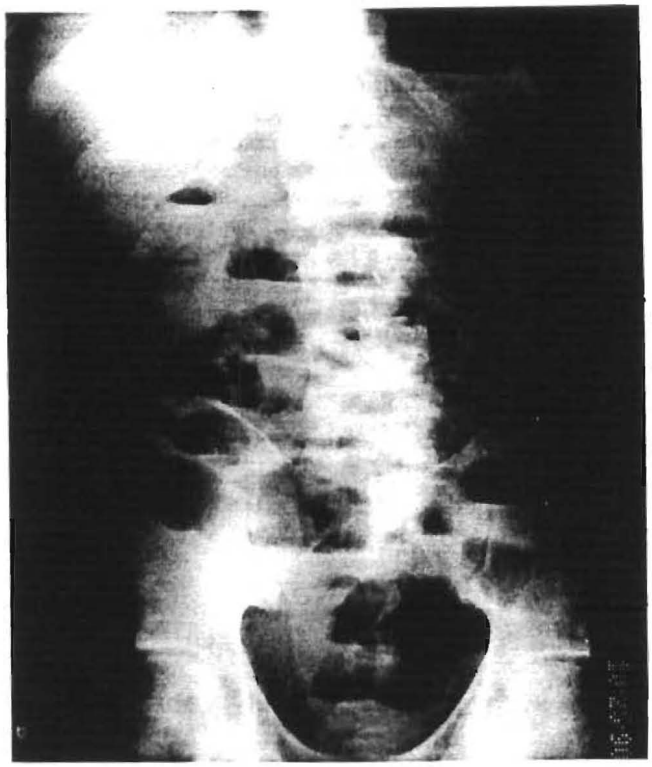


Figure 5: Erect abdominal films at the time of rejection. Notice the multiple fluid levels.

Table 1
Time, Severity and Treatment of Intestinal Graft Rejection

Total Number		Histological Degree of Rejection (Postop. days)			Treatment of Rejection (Postop. days)			
						Steroid		
Biopsy	Rejection	None	Mild	Prominent	Increase FK-dose	Bolus	Recycle	OKT322
22	10 (45%)	21,28 35,37 78,127 151,177 197,217 247,378	7,59,71 92,437 453,486 569	14,66	59,92 166	14,35 166,437 569	166,437	14

Figure 6: Upper GI series of normal (A, above) and rejected (B, right) graft. Notice distention of the intestinal loops and effacement of the mucosal folds at the time of rejection.

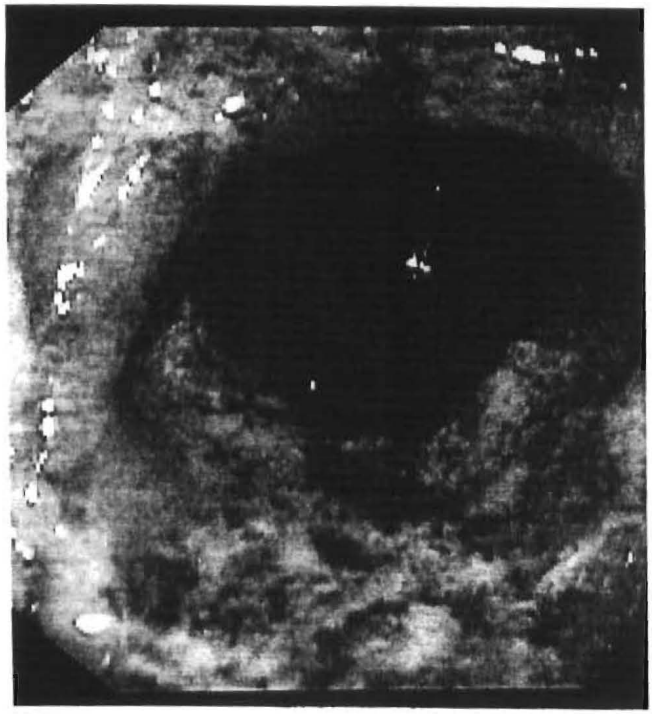


Figure 7: Endoscopic picture of rejected small bowel graft (terminal ileum) showing partial sloughing of the intestinal mucosa and pseudomembrane formation.

hospitalization period (five months), which were treated just with increases in FK 506 doses. (Table 1)

On October 9, 1990, the patient was discharged from the hospital enjoying full unrestricted oral diet with no gastrointestinal complaints and normal endoscopic, histologic and metabolic studies. One week later, the patient was readmitted with frequent copious vomiting, severe diarrhea, persistent abdominal pain and septic shock-like syndrome. The erect abdominal x-ray films showed multiple fluid levels with no radiological evidence of pneumatosis or free air in the peritoneal cavity. (Fig. 5) The barium follow-through study demonstrated dilated edematous intestinal loops, prolonged transient time and abnormal mucosal pattern with no signs of mechanical obstruction. (Fig. 6) The endoscopic examination showed extensive sloughing of the intestinal graft mucosa (Fig. 7) and the histologic findings documented prominent rejection. On the day of admission the FK 506 plasma level was undetectable (< 0.1 ng/mL) and the patient admitted that he stopped taking his immunosuppressive drugs for the last five days. The patient was then immediately treated with 1 gm Solumedrol and a steroid cycle together with the reinstitution of FK 506 therapy. The clinical, endoscopic, histologic and metabolic recovery of the graft was very slow with persistent histological evidence of intramural graft infection, pseudomembrane formation, abnormal d-xylose and vitamin E absorption tests. Six months later the graft biopsy showed intact intestinal mucosa and apparent normal villi. The last four endoscopic biopsies, however, showed variable degrees of focal cryptitis associated with persistent submucosal histopathological changes.

Infection. Despite the frequent clinical and/or histological intestinal graft rejections, the patient experienced only one episode of bacterial translocation. On POD 58 he developed high fever and hemodynamic evidence of fulminant systemic sepsis. Repeated blood cultures were positive for both *Candida albicans* and *Enterococcus faecalis*. The same organisms were simultaneously isolated from multiple stool cultures at a concentration of greater than $10^9/cc^3$. Meanwhile, the intestinal graft biopsy showed mild acute cellular rejection with focal sloughing of the cell surface epithelium. The patient was successfully treated with the proper systemic antibiotics including a full course of amphotericin B, selective intestinal decontamination and augmented immunosuppressive treatment.

Graft Dysfunction. Recovery of the intestinal graft motility was clinically and radiologically evident after the first 10 postoperative days. The achievement of alimentation was a slow process, despite early initiation of both enteral feeding (POD 7) and oral FK 506 therapy (POD 19), requiring concomitant intermittent intravenous nutrition for almost eight months. (Fig. 3) The serial body weight measurements, d-xylose absorption test, fat digestion, serum zinc and vitamin levels were optimal until the patient stopped his immunosuppressive treatment. Subsequent recovery of the graft was slow and incomplete requiring cyclic TPN therapy.

The Question of Chronic Rejection. The current nutritional, endoscopic, histologic and radiologic data are suggestive of chronic graft changes particularly in the distal ileum. Full thickness biopsies and further longitudinal follow-up studies are necessary to establish the diagnosis of chronic rejection and determine the irreversibility of graft dysfunction.

Commentary
James Williams

This paper presented by the group founded by Dr. Thomas Starzl illustrates the formidable barriers presented by intestinal transplantation. While the groups at London, Ontario, Chicago and Pittsburgh have shown that inclusion of the liver with an intestinal graft remarkably reduces the risk of bowel rejection, the isolated bowel graft appears to defy available immunosuppressive therapy. The groups in France and Germany have reported patients with isolated intestinal grafts who have been freed of dependence on parenteral nutrition for variable periods of time, but the failures substantially outnumber the successes.

Despite the use of high doses of potent immunosuppression in the patient described, doses which appear to have jeopardized the patient's renal function and exposed him to near lethal infection and despite inclusion of the entire immunosuppressive armamentarium available to the transplant surgeon (azathioprine, FK 506, corticosteroids, OKT3), this patient continued to relentlessly reject the bowel so that its functional integrity has been essentially lost. While these authors are to be commended for their tenacity and clinical skill in bringing this patient through these difficult complications and lucidly describing the problems encountered, it appears that the tools currently available to alter human alloreactivity are inadequate to support the function of an intestinal allograft. As the new drugs, monoclonal antibodies and tolerance strategies expand the contemporary literature, the barriers to successful intestinal transplantation will gradually recede through the efforts of courageous patients and physicians such as described by Dr. Abu-Elmagd.