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Multivisceral Transplantation: Introducing a Therapeutic Option for End-Stage Short Bowel Syndrome With Combined Organ Failure

Aim: To report an exemplary series of selected multivisceral transplants (MVTx), partly including right kidney and ascending colon in patients with complicated end-stage short bowel syndrome (SBS).

Methods: Three patients suffering from short bowel syndrome and massive adhesions after multiple abdominal operations ("frozen abdomen") due to fistulizing Crohn´s disease (CD), malrotation, and trauma after motorcycle accident underwent MVTx including stomach, pancreatoduodenal complex, liver, intestine, in one patient plus ascending colon, right kidney, right adrenal gland, and greater omentum, and in another patient plus right kidney and adrenal gland. Immunosuppression consisted of alemtuzumab, tacrolimus and steroids in one patient, and thymoglobuline, tacrolimus, steroids, and infliximab in the two other patients.

Results: All patients were off parenteral nutrition by postoperative week 3. The patients recovered completely and were discharged 2.5, 4, and 6 months after MVTx, respectively. All patients are doing well 57, 13, and 9 months after MVTx, respectively.

Conclusion: MVTx respresents the ultimate therapeutic option in end-stage SBS complicated with end-stage liver disease, massive adhesions, and associated organ failures, such as chronic pancreatitis, and chronic kidney failure.

Key words:
multivisceral transplantation, short bowel syndrome

Multiviszeraltransplantation – eine therapeutische Option für Patienten mit terminalen Kurzdarmsyndrom und gleichzeitigem Organversagen

Ziel: *Es wird über ausgewählte Multiviszeraltransplantationen (MVTx), teilweise einschließlich der rechten Niere und Colon ascendens, bei Patienten mit terminalem Kurzdarmsyndrom (SBS) berichtet.*

Methoden: *Drei Patienten, die unter einem Kurzdarmsyndrom und massiven Adhäsionen nach multiplen Bauchoperationen ("frozen abdomen") infolge fistelbildendem Morbus Crohn (CD), Malrotation und Trauma durch Motorradunfall litten, unterzogen sich einer MVTx einschließlich Magen, pankreaduodenalem Komplex, Leber, Darm, bei einem Patienten zusätzlich Colon ascendens, rechte Niere, rechte Nebenniere und Omentum majus sowie bei einem anderen Patienten zusätzlich rechte Niere und Nebenniere. Die Immunsuppression bestand bei einem der Patienten aus Alem-*

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tuzumab, Tacrolimus und Steroiden und bei den anderen beiden Patienten aus Thymoglobulin, Tacrolimus, Steroiden und Infliximab.
Ergebnisse: Bei allen Patienten konnte die parenterale Ernährung in der 3. postoperativen Woche abgesetzt werden. Die Patienten erholten sich vollständig und wurden 2 $^1/_2$, 4 bzw. 6 Monate nach MVTx aus dem Krankenhaus entlassen. Es geht allen Patienten 57, 13 bzw. 9 Monate nach MVTx gut.
Schlussfolgerung: Die MVTx stellte die letzte therapeutische Option beim terminalen SBS mit terminalem Leberversagen, massiven Adhäsionen und gleichzeitig vorliegendem Organversagen, wie z. B. chronischer Bauchspeichelentzündung und chronischem Nierenversagen, dar.

Schlüsselwörter:
Multiviszeraltransplantation, Kurzdarmsyndrom

Introduction

Multivisceral transplantation (MVTx) has been attempted since the idea of small bowel transplantation became a clinical reality. Starzl and Kraupp performed the first experimental MVTx in 1960 [1]. Starzl was also the first to perform a MVTx clinically in 1983 and 1986 [2]. Williams contributed another two MVTx patients whom he reported on in 1989 [3]. However, success rates were disappointing with two patients dying early after surgery due to uncontrollable bleeding and the other two due to lymphoma 3 and 6 months after transplantation. Margreiter et al [4] performed the first MVTx in an adult patient who left hospital free of total parenteral nutrition (TPN). Along with the slow but steady development of intestinal transplantation (ITx) since the late 1980s, the number of MVTx increased as well. Ninety-six MVTx had been reported to the Intestinal Transplant Registry before September 2001, accounting for approximately 13.6% of all intestinal transplants [5]. Because the term MVTx is defined as transplantation of three or more visceral organs en-bloc, there is a considerable variation in number and combination of organs grafted. Simultaneous MVTx and kidney transplantation (KTx) have been reported episodically [6-8], however none of them was performed in combination with parts of the colon as described in the first of the subsequent case reports. In the following we report three exemplary case reports in order to describe characteristical indications, potential complications, and outcome.

Case Report 1

A 36-year old female patient was referred to our centre in June 2003 after continuous hospital stay over more than 1.5 years to undergo combined liver and intestinal transplantation because of very short bowel syndrome (15cm residual jejunum) and total parenteral nutrition (TPN)-associated liver cirrhosis. Fistulizing CD was diagnosed in 1988. In November 2001 subtotal colectomy had been performed which was followed by postoperative ileus, recurrent intestinal leakages, recurrent anastomotic leakages with abdominal sepsis and multiple abdominal reoperations resulting in sequential subtotal small bowel resection. TPN was instituted in April 2002 leading to cholestatic liver disease rapidly. TPN-associated progressive liver cirrhosis with severe portal hypertension was diagnosed in autumn 2002. After a total of over 20 operations, the patient suffered from dehiscence of the abdomenal wall until June 2003, when she was referred to our institution. Urgent reoperation because of intraabdominal bleeding revealed extensive intra-abdominal scaring in terms of a frozen abdomen with complete obstruction of the abdominal cavity by the residual mesentery, extensive scaring of the retroperitoneum and an approximately 10 cm dehiscence of the abdominal wall. The indication for en-

bloc MVTx was confirmed. In the following 5 months, the patient suffered from recurrent decompensations of liver and kidney function requiring repeat hemodialysis and bioartificial liver support. After 5 months on the waiting list, MVTx including stomach, pancreato-duodenal complex, small bowel, right hemicolon, liver, right kidney, the adjacent right adrenal gland, and the greater omentum was performed using standard techniques [9].

The recipient operation was dominated by a meticulous surgical approach. Since the whole abdominal cavity and retroperitoneum were filled with massive collaterals because of severe portal hypertension which also explained the daily parastomal bleeding episodes prior to MVTx, major blood losses during dissection and exenteration of the abdominal cavity occurred although a veno-venous bypass was used. Vascular reconstruction was accomplished by interpositon of the retrohepatic caval vein including the right renal vein into the recipient caval vein (CV) using standard end-to-end anastomosis of the suprahepatic inferior CV and the infrahepatic CV between the insertion of the right donor renal vein (RV) and recipient RV. Arterial reconstruction was performed using the donor abdominal aorta with the natural offsprings of the celiac axis, superior mesenteric artery, and right renal artery, which was anastomosed to the recipient´s aorta at the site of the original celiac axis. Following reperfusion, the gastrointestinal continuity was restored by a cardio-fundostomy and a terminal colostomy of the transplanted right hemicolon.

The abdomen had to be closed temporarily by an alloplastic mesh (Vicryl mesh®; Ethicon, Norderstedt, Germany) because of a preexisting massive incisional hernia, and skin closure was achieved only 7 days after transplantation.

Immunosuppression consisted of alemtuzumab (Campath 1H, Genzyme, Neu-Isenburg, Germany), tacrolimus (Astellas GmbH, Munich, Germany) and steroids. Early enteral immunonutrition was initiated on postoperative d 1. The patient was off TPN by postoperative week 3. She experienced an episode of pneumonia caused by citrobacter and enterococcus species which required tracheostomy and mechanical ventilation for 4 weeks. The patient was discharged 2.5 months after MVTx, with

excellent graft function of all transplanted organs.

The further course was complicated by acute cellular rejection approximately 4 months after MVTx, which was responsive to steroid pulse therapy and new onset of sirolimus (Rapamune, Wyeth Pharma GmbH, Münster, Germany), however, followed by one episode of CMV-enteritis. Shortly thereafter, a tissue invasive aspergillosis of the left sphenoid and ethmoid sinusoids was detected on the basis of headaches refractory to analgesics. A complete diagnostic workup revealed invasive pulmonary aspergillosis and osteitis of the lateral sphenoid wall with an inflammation of the left cavernous sinus, inflammatory stenosis of the internal carotid artery, and abducent nerve with subsequent paralysis and double visions. Under an almost 1,5-year therapy with various anti-fungal regimens, a complete recovery was achieved until August 2005, leaving the patient without any neurological residues.

The patient is currently heading her fifth transplant anniversary in excellent clinical condition, has achieved full physical and social rehabilitation and is contributing in office matters to the family's house painting business.

Case Report 2

A 25-year old male patient with ultra-SBS due to congenital intestinal malrotation type I and multiple abdominal operations in early childhood leading to a duodeno-transversostomy in 1985, frozen abdomen, and long-term dependency on total parenteral nutrition (TPN) underwent MVTx and kidney transplantation (stomach, duodenum, pancreas, liver, intestine, right kidney and adrenal gland) in July 2007 because of TPN-induced end-stage liver cirrhosis, chronic necrotizing pancreatitis, and chronic renal insufficiency.

The operation was carried out under hemodynamically stable conditions. After completion of the cava anastomosis, an arterial reconstruction was performed by means of a Carrel´s patch of the donor aorta onto the recipient aorta. Following reperfusion gastrointestinal continuity was restored by cardio-fundostomy and ileo-sigmoidostomy. The distal end of the intestine was brought out as Bishop-Koop-Ileostoma for monitoring purposes. The abdomen,

which had been opened with a midline and flank-to-flank incision could not be closed primarily. A temporary closure with a Vicryl mesh was performed instead. Complete abdominal closure required three further re-operations.

Initial immunosuppression comprised tacrolimus (Astellas, Munich, Germany), steroids in association with thymoglobulin (Genzyme, Neu-Isenburg, Germany) and infliximab (Remicade, Essex Pharma, Munich, Germany) induction therapy. Postoperative organ function recovered rapidly and completely. Tracheostomy was performed due to prolonged weaning because of muscular weakness and respiratory infections.

The patient experienced one episode of fungal pneumonia caused by *aspergillus fumigatus* which responded to combined treatment with caspofungin and voriconazole. Along with respiratory and abdominal infections caused by *enterococcus faecium* and gram-negative bacteria that required antibiotic treatment, a non-invasive CMV-infection prompted antiviral therapy. There was an isolated acute cellular rejection of the kidney-transplant responding well to steroid pulse therapy and a short episode of indeterminate for rejection of the intestine.

Two months post transplantation, the patient presented with crescendo-type lumbalgy which was attributable to spondyldiscitis. Considering *enteroccus faecium* and *aspergillus fumigatus* as potential pathogens, both of which had challenged the patient during the initial intensive care period, calculated antibiotic and antifungal treatment was conducted. On account of aggravating lumbalgy, rising CRP-levels of 20 mg/dl and progression of vertebral body destruction approximately six weeks after onset of symptoms, surgical restoration was deemed necessary. Intraoperatively the L2-L3 disc was found to be sequestered. Apart from the complete removal of abundant necrotic disc material, a posterior stabilization inserting an internal fixateur system screwed into the vertebral bodies between L1 and L4 and a reconstruction of the defect with an autologous iliac crest graft was performed.

Direct smear and culture of the spine taken intraoperatively yielded *aspergillus fumigatus* which gave evidence to an invasive fungal infection. The patient recovered completely under

triple antifungal treatment consisting of caspofungin, voriconazole, and liposomal amphotericin B.

At present, 8 months after transplantation and 5 months after spinal surgery, there is a complete absence of clinical symptoms and significant signs of inflammation. The patient underwent closure of the ileostomy 7 months after transplantation and is completely off TPN and parenteral fluids.

He is now heading his 1.5-year transplant anniversary and will commence a course of studies at the university.

Case Report 3

A 35-year old male patient with ultra-SBS, end-stage liver cirrhosis, necrotizing pancreatitis, and extensive abdominal scaring with wide dehiscence of the abdominal wall due to a motorcycle accident in June 2006 underwent MVTx (stomach, duodenum, pancreas, liver, intestine) in November 2007. The patient had experienced multiple injuries including complete rupture of the mesentery root with infarction of the complete small intestine and right portion of the large intestine, pancreatic contusion, and multiple liver lacerations. Due to multiple complications comprising tertiary peritonitis with methycillin-resistant staphylococcus aureus (MRSA), MRSA pneumonia, duodenal fistula, necrotizing pancreatitis and rapidly progressive cholestatic liver disease, the patient had been operated multiple times, staying in hospital over 16 months continously. Additionally, paralysis of the right radial nerve due to fracture of the right humerus with subsequent pseudarthrosis developed. The patient was transplanted in severly impaired state of health with bilirubin levels exceeding 20 mg/dl and was carrier of two multi-resistent bacteria, multiresistant pseudomonas aeruginosa and MRSA, in November 2007.

Operative procedures were conducted as described above. Evisceration of the entire abdomen apart from the sigmoid colon revealed massive intraabdominal scaring after peritonitis and necrotizing pancreatitis, as well as two duodeno-cutaneous fistula. The multivisceral transplant consisted of liver, stomach, duodenum, pancreas, and small bowel. After establishing vascular supply to the grafts (Carrell´s patch; caval interposition), the enteral continuity was ac-

complished by a end-to-side cardio-fundostomy, a side-to-side ileosigmoideostomy, and the terminal ileum was brought out as Bishop-Koop ileostomy. The abdomen, which had been opened by a midline and flank-to-flank incision was closed temporarily and covered using a vaccum-assisted wound closure system (V.A.C.; KCI GmbH, Wiesbaden, Germany). Complete closure required several reoperations. Initial immunosuppression comprised tacrolimus (Astellas, Munich, Germany), steroids in association with thymoglobulin (Genzyme, Neu-Isenburg, Germany) and infliximab (Remicade, Essex Pharma, Munich, Germany) induction therapy. Enteral nutrition started 6 hrs after transplantation and complete independence from intravenous nutritional supplementation was achieved around 3 weeks after MVTx.

The postoperative course was complicated by a pancreatic fistula due to a circumscript pancreatitis of the transplanted pancreatic tail leading to peritonitis. Several abdominal lavages were performed including the insertion of catheters to the pancreatic tail in order to perform continuous intraabdominal lavage. Secondary to pancreatic fistula, a localized insufficiency of the gastric anastomosis developed requiring operative revision. Apart from the surgical complications and difficulties in wound closure, the patient required tracheotomy, partly owing to muscular weakness, however particularly due to pneumonia and peritonitis caused by multiresistant pseudomonas for which the patient was carrier prior to transplantation. Further difficulties arose from a steroid resistant acute cellular and humoral rejection which relapsed several times, requiring plasmapheresis, thymoglobulin, and infliximab therapy. The patient was finally discharged approximately six months after multivisceral transplantation in good general state of health.

The patient is currently heading his first transplant anniversary in excellent clinical condition, and has achieved good physical and social rehabilitation.

MVTx represents the ultimate therapeutic option in end-stage SBS complicated with end-stage liver disease, massive adhesions, and associated organ failures, such as chronic pancreatitis, and chronic kidney failure [10].

Our three clinical case reports represent typical histories of patients suffering from end-stage SBS who are being referred to our transplant program. The latter comprises an experience of 25 intestinal and multivisceral transplants in total.

MVTx is defined as removal and replacement of both native foregut and midgut [11] including the stomach. Grafts without stomach are, by definition, not registered as multivisceral grafts in the Intestinal Transplant Registry. The inclusion of the liver, however, is optional. In the course of MVTx the native abdominal viscera are resected and the graft is transplanted en bloc. The arterial blood supply is typically reestablished by a Carrel's patch or end-to-side onto the recipient aorta using the segment of the donor aorta that contains the orifices of the celiac axis and the superior mesenteric artery (SMA). Venous drainage varies according to the inclusion or exclusion of the liver. If so, the venous drainage of the whole graft is achieved either piggy back or through interposition of the retrohepatic caval portion. Otherwise, portal drainage may be established into the portal system or into the inferior caval vein. Apart from the liver, kidneys, adrenal glands, and large intestine of the donor may or may not be included depending on the individual needs of the respective patient [9].

Until recently, a common requirement of multivisceral transplantation has been removal of the native duodenum, pancreas and spleen in the process of abdominal exenteration. Modified multivisceral transplantation with splenopancreatic preservation procedures were proposed by two groups [12,13]. Frequently, though, the indications for their removal were rather anatomical reasons than underlying disease states in those organs. In the modified multivisceral technique, the native spleen and pancreas are preserved with venous outflow through a native portocaval shunt, and native pancreatic exocrine drainage is established to the donor jejunum. Risk of transplant pancreatic insufficiency, post transplant lymphoproliferative disorder, and post-splenectomy sepsis may be avoided utilizing this technique. However, there is some ongoing dispute on nomenclature issues. Because the nomenclature of grafts containing the intestine is based on the type and number of the allograft-ed rather than the explanted organs, it was argued that splenopancreatic preservation should not be classified as modified multivisceral transplantation. In a series of multivisceral adult recipients, Abu-Elmagd et al. [14] described a propensity for better graft survival among those 14 patients undergoing modified MVTx with splenopancreatic preservation as compared with a total of 11 contemporaneous modified MVTx with spleno-pancreaticoduodenectomy. Preservation of the native spleen and pancreas abolished deleterious infectious complications, cases of PTLD and GVHD, as well as post transplant endocrine and exocrine pancreatic insufficiency. In contrast, their removal was followed by two cases each of GvHD and PTLD, and the fact that overwhelming post-splenectomy infectious complications were the leading cause of death [14].

Despite the profound morbidity of patients, which is exemplarily described in this series of case reports, MVTx is performed in increasing numbers and the one-year graft and patient survival as well as the conditional post-1-year survival rates are at least as good as the other forms of intestinal transplantation [9,15]. Apart from pre-operative morbidity of patients owing to liver failure, kidney failure, frequent infectious complications with multiresistant bacteria and fungi, post-transplant immunological and infectious complications, lack of sufficient abdominal domain and preexisting damage to the abdominal wall owing to multiple surgical procedures represent major sources of post-transplant morbidity.

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