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ORIGINAL ARTICLE

The 'Blind Innsbruck Ostomy', a cutaneous enterostomy for long-term histologic surveillance after small bowel transplantation

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Summary

Intestinal transplantation has evolved into an established treatment for patients with intestinal failure. Although acute rejection episodes are reversible, late onset and chronic rejections remain major prognostic factors. We describe here our experience with endoscopic and histologic long-term monitoring through a cutaneous enterostomy. Between 1989 and 2003, 24 intestinal transplants were performed. After revascularization and reconstruction of proximal intestinal continuity, a side-to-end ileo-enterostomy was performed 20 cm from the stoma and the terminal allograft ileostomy left in the abdominal wall. Approximately after 2 months, in eight patients (nine transplants), the stoma was excluded from the gastrointestinal continuity, allowing ongoing endoscopy and histologic examination. Of 280 forceps biopsies, 64 (23%) were performed through the 'blind ostomy'. Eleven acute allograft rejections were diagnosed between days 3 and 51, with two episodes in three cases. Through the 'blind ostomy', a late mild acute rejection was diagnosed in five instances, three to 37 months after transplantation. In all these patients, basal immunosuppression was intensified. Chronic rejection was seen in three cases 4–26 months after transplantation. In one of the three patients, chronic rejection was diagnosed from the excluded blind enterostomy. A long-term cutaneous enterostomy, even if disconnected from the intestinal continuity, enables simple long-term monitoring of small bowel allografts.

Introduction

Progress in surgical technique and the introduction of new immunosuppressive drugs have established intestinal transplantation as a life-saving therapy for patients with intestinal failure and suffering complications from total parenteral nutrition [1–5]. By the end of 2006, more than a thousand intestinal transplantations world-wide had been performed as isolated small bowel grafts, combined liver and intestinal grafts or multivisceral transplants defined as the *en bloc* transplantation of three or more abdominal organs. In the period after 2000, the 1- and 5-year patient and graft survival rates reported by the Intestinal Transplant Registry were approximately 80% and 65%, and 60% and 45%, respectively [6]. After standardization of the surgical procedure, rejection and infection are the major risk factors for graft loss and patient survival, making intestinal transplantation one of the most complex immunologic challenges. The incidence of acute rejection varies between 40% and 80%, although

important progress has been achieved with tacrolimus-based immunosuppression and induction therapy using thymoglobulin, interleukin-2-receptor antagonists as well as campath-1H [7]. Furthermore, the use of rapamycin has demonstrated a significant influence on the incidence of rejection and it seems to have an important benefit for long-term function [8]. Although acute rejection episodes are reversible in most cases, late onset and chronic rejection are still negative prognostic factors [2,3]. As rejection seems to be unpredictable, an important feature for long-term outcome is reliable immunologic monitoring, even in the later post-transplant period.

Histology is the gold standard for monitoring after small bowel transplantation. Although histopathologic abnormalities are often patchy and occur in grossly normal mucosa, general spreading of rejection in the small bowel is already detectable in its earliest stage [9,10]. Following multivisceral transplantation, however, the stomach is an exception, as normal histology cannot exclude small bowel rejection [3]. Therefore, biopsies from the enterostoma are representative and accepted as standard. Although the diagnosis and severity of acute rejection are well understood and classified, data on chronic immunologic graft dysfunction are rare [11], probably because (i) biopsies are not easy after reconstruction of the continuity of the graft with the patient's own gut and (ii) it is difficult to find alterations in mucosal specimens caused by chronic rejection. Chronic rejection is characterized by obliterative arteriopathy of the mesenteric vessels and atrophy of the intestinal wall [12]. Both problems can be easily addressed using the new surgical technique described below.

Patients and methods

Between December 1989 and December 2003, 24 small bowel transplantations were performed in 20 patients (isolated small bowel, $n = 15$; multivisceral transplants, $n = 9$). Patient characteristics are given in Table 1. All but one of the intestinal allografts was obtained from ABO blood type-identical deceased donors. In one case, a living-related small bowel transplantation was performed. HLA matching was random, but lymphocytotoxic cross-match was negative in all patients. Induction therapy was started pre-operatively, either with thymoglobulin (2 mg/kg/day, Sangstat®; SangStat Medical Corporation, Freemont, CA, USA) or interleukin-2-receptor antagonists (daclizumab 2 mg/kg/day or basiliximab 20 mg/day, day 0 and 4). Postoperative immunosuppression, except in the first patient who received cyclosporine A, was based on tacrolimus, steroids, and azathioprine. Tacrolimus trough level was targeted between 15 and 20 ng/ml (microparticle enzyme immunoassay technology) in the first postoperative month, at 15 ng/ml until month 3 and then around 10–15 ng/ml in the first year. Methylprednisolone (500 mg i.v. bolus) was administered 15 min before graft reperfusion followed by a rapid prednisone taper to 25 mg on day 10, reducing the dosage by 5 mg every 2 weeks until 5- to 10-mg maintenance therapy for 3–6 months. Azathioprine (1–2 mg/kg/day) was added according to the white blood cell count 12 h after reperfusion of the graft. Acute rejection was treated with i.v. methylprednisolone bolus (500 mg over three consecutive days) and optimization of tacrolimus levels. Thymoglobulin was administered for 5–7 days in two patients with steroid-resistant rejection. After 2002, rapamycin (Rapamune, Wyeth, Madison, NJ, USA) was added 3–6 months following transplantation to replace steroids and azathioprine. Trough levels of tacrolimus and rapamycin were between 5 and 10 ng/ml.

Surgical technique

After preparing an adequate abdominal cavity and isolating the superior mesenteric or portal vein and infrarenal aorta for orthotopic transplantation or the inferior vena cava – if a heterotopic implantation technique was planned – the small bowel was revascularized. Following reperfusion of the graft, the upper intestinal reconstruction was performed using an end-to-end or side-to-side entero-enterostomy, depending on the situation. Multivisceral transplantation was performed according to the described standard procedure [3,13].

If part or the whole recipient colon was available, a side-to-end ileocolostomy was performed 20 cm from the end of the graft. The distal end of the graft was then brought out as a stoma at the appropriate site, which is usually in the right lower quadrant of the abdominal wall. If no colon or rectum was available, a terminal ileostomy was performed.

Following observations, made by using the Thiry–Vella loop, where amongst others luminal factors are not essential for maintenance of normal cellular turnover [14,15]. We introduced the concept of the excluded ostomy for long-term immunologic surveillance. From the sixth patient onwards, in nine transplants, if technically feasible, and after informing the patient in detail, the enterostomy was excluded from the gastrointestinal continuity after clinical and immunologic stabilization and left for long-term histologic follow-up for at least 1 year (Table 2). Surgical preparation in this case is carried out by following the small bowel graft from the stoma toward the entero-enterostomy with the patient's colon. The gut is then disconnected, keeping the blood supply intact with a stapler device (GIA) and both ends are oversewn. The now excluded 20-cm-long small bowel segment is again reinserted in the abdominal

Table 1. Consecutive number of transplants, patient characteristics, indication for transplantation, type of grafts, immunosuppression, surgical and infectious complications as well as outcome after intestinal transplantation.

No.	Age	Gender	Disease	Tx	Immunosuppression (Induction, long term)	Surg. complication	Infection	Outcome
1	48	M	Pancreatic cancer	MVTx	ATG, CyA, Aza, P CyA, Aza, P		CMV-enteritis	9 months, tumor recurrence†
2	51	M	Intestinal pseudo-obstruction	SBTx	ATG, FK, Aza, P FK, Aza, P		CMV-enteritis	11 months, MOFS†
3	41	W	Gardner syndrome	MVTx	ATG, FK, Aza, P FK, Aza	Biliary leakage		Alive, 95 months
4	62	M	NET pancreas with liver metastases	MVTx	ATG, FK, Aza, P FK, Aza, P			42 months, tumor recurrence†
5	66	M	HCC, HCV-cirrhosis, thrombosis splanchnic veins	MVTx	Dac, FK, Aza, P FK, Aza	Pancreatitis, arrosion of aortic conduit		29 days, pancreatitis†
6	35	M	SBS – M. Crohn	SBTx	ATG, FK, Aza, P FK, Rapa			Alive 81 months
7	39	M	SBS - mesenterial vein thrombosis	SBTx	Bas, FK, Aza, P FK, Aza, P	Laparocele	Sepsis, central line	3 months, MOFS†
8	10	M	SBS – volvulus	SBTx living related	Bas, FK, Aza, P FK, Aza, P	Aneurysma arterial conduit – thrombosis	Candida pneumonia	Retransplantation
9	2	W	SBS – tumor of the yolk sac	SBTx	Bas, FK, Aza, P FK, Aza, P		Sepsis	Retransplantation
10	10	M	Arterial thrombosis	(8) ReTx SBTx	FK, Aza, P FK, Aza, P	Acute liver failure – LTx	Fungal sepsis	11 months, MOFS†
11	48	M	SBS – mesenteric vein thrombosis	SBTx	Bas, FK, Aza, P FK, Aza, P	Intestinal obstruction	CMV-enteritis, pneumonia	10 months, aspergillosis†
12	36	W	SBS – M. Crohn	SBTx	ATG, FK, Aza, P FK, Aza	Bleeding		Retransplantation
13	38	W	Gardner syndrome	MVTx	Dac, FK, Aza, P FK, Aza, P			Retransplantation
14	38	W	Chronic rejection	(12) ReTx SBTx	FK, Aza, P FK, Aza		Sepsis – nocardia	8 months, MOFS†
15	24	W	Intestinal pseudo-obstruction	SBTx	ATG, FK, Aza, P FK, Rapa			Alive 41 months
16	38	M	SBS - volvulus	SBTx	ATG, FK, Aza, P FK, Rapa			Alive 39 months
17	38	M	Gardner syndrome	SBTx	ATG, FK, Aza, P FK, Rapa		CMV-enteritis	Alive 39 months
18	38	W	Chronic rejection	(13) ReTx SBTx	FK, Aza, P FK, Rapa	Abdominal wall reconstruction	Sepsis, renal insufficiency	Alive 35 months
19	9 months	W	SBS – M. Zülzer Wilson	MVTx	Bas, FK, Aza, P FK	Abdominal wall reconstruction		Alive 33 months

Table 1. continued

No.	Age	Gender	Disease	Tx	Immunosuppression (Induction, long term)	Surg. complication	Infection	Outcome
20	5	W	Chronic rejection	(9) ReTx MVTx	FK, Aza, P FK, Rapa	Abdominal wall reconstruction		Alive 29 months
21	4	W	SBS – volvulus	SBTx	ATG, FK, Aza, P FK, Aza, P	Abdominal wall reconstruction		4 months, PTLD†
22	60	M	HCC, HCV-cirrhosis, thrombosis splanchnic veins	MVTx	ATG, FK, Aza, P FK, Rapa	Tumor recurrence (HCC)		Alive 28 months
23	60	W	SBS – M. Crohn, renal insufficiency	SBTx/NTx	ATG, FK, Aza, P FK, Aza, P	bowel obstruction, graft removal	CMV, pneumonia PTLD	6 months, MOFS†
24	21	W	Gardner syndrome	MVTx	ATG, FK, Aza, P FK, Aza, P		Peritonitis	4 months, sepsis, MOFS†

SBTx, small bowel transplantation; MVTx, multivisceral transplantation; ReTx, retransplantation; SBS, short bowel syndrome; LTx, liver transplantation; NET, neuroendocrine tumor; NTx, kidney transplantation; CMV, cytomegalovirus; MOFS, multiorgan failure syndrome; PTLD, post-transplant lymphoproliferative disease; ATG, antithymocytoglobulin; CyA, cyclosporine A; FK, Prograf; Aza, azathioprine; P, steroids; Rapa, rapamycin; Dac, daclixumab; Bas, basiliximab.

wall (Fig. 1). Later, the 'blind small bowel segment' was easily resected without laparotomy.

Endoscopy

Endoscopy and biopsies were performed every second day for the first month, twice weekly during the second month and weekly in the third month. Thereafter, depending on the postoperative course and the immunologic risk, one to two endoscopies were performed per month. During every endoscopy, at least two biopsies were taken from two different sites away from suture lines to avoid false interpretation of histology caused by mechanical alterations. Endoscopies were also carried out daily in the event of clinical suspicion of rejection until resolution. Despite the continued macroscopic evaluation of the mucosa, zoom video endoscopy was recently introduced and has permitted targeted biopsies to be taken. After modification of the stoma into the blind-ending enterostomy, mucosal and also deep transmucosal biopsies were taken in patients with graft dysfunction or signs of chronic rejection.

Histology

All specimens were fixed in 10% formalin, dehydrated to xylene with graded alcohols and paraffin-embedded. Per biopsy ten 4-μm serial sections were stained with hematoxylin-eosin and also analyzed with trichrome stains and immunohistology when needed. Antibodies used for immunohistologic investigation were commercially available monoclonal antibodies against CD3, CD20, CD68, and cytomegalovirus (CMV). All microscopic slides were examined by two gastrointestinal pathologists.

Histopathologic analysis included assessment of the mucosa and, when present, of all deeper layers of the bowel wall. The mucosal architecture, abnormalities of the epithelium, inflammation by either mononuclear cells and/or granulocytes, intra-epithelial lymphocytes (IEL), mucosal crypt apoptosis, and abnormalities of the vasculature were recorded for every biopsy. Acute cellular rejection was graded as suggested by Wu *et al.* [16]. Grade 0 was normal. Grade 1 was used for cases with more than six apoptoses per 10 crypts. Grade 2 indicated a confluence of crypt apoptosis and Grade 3 severe rejection with ulceration of the mucosa. Cases with a slight increase in crypt apoptosis but less than six per 10 crypts were designated suspicious for acute cellular rejection. Chronic rejection was defined by mononuclear infiltration and fibrosis of the deeper layers of the bowel wall in conjunction with myointimal thickening of arterial vessels. Theses changes were semi-quantitatively graded on a scale from 0 to 2 as previously suggested [12].

Table 2. Consecutive number of transplants with 'blind ostomy', age and indication for transplantation, type of grafts, time of transplantation, time of reconstruction – resection of blind ostomy and outcome.

No.	Age	Disease	Tx	Transplantation	'Blind ostomy'	Resection ostomy	Outcome
6	35	SBS – M. Crohn	SBTx	August 1998	October 1998	=>	Alive and ostomy *in situ*
9	2	SBS – tumor of the yolk sac	SBTx	December 1999	February 2000	January 2002	Chronic rejection => Re-Tx (11/2002)
10	10	(No. 8) Arterial thrombosis	Re-SBTx	January 2000	March 2000	=>	Dead with ostomy (sepsis)
11	48	SBS – mes. vein thrombosis	SBTx	February 2000	April 2000	=>	Dead with ostomy (sepsis)
15	24	Intestinal pseudo-obstruction	SBTx	August 2001	November 2001	November 2004	Alive
16	38	SBS – volvulus	SBTx	February 2002	June 2002	May 2003	Alive
20	5	(No. 9) Chronic rejection	Re-MVTx	November 2002	March 2003	April 2004	Alive
21	4	SBS – volvulus	SBTx	January 2003	March 2003	=>	Dead with ostomy (post-transplant lymphoproliferative disease)
22	60	HCC, HCV-cirrhosis, thrombosis splanchnic veins	MVTx	February 2003	May 2003	February 2004	Alive

SBTx, small bowel transplantation; MVTx, multivisceral transplantation; SBS, short bowel syndrome.

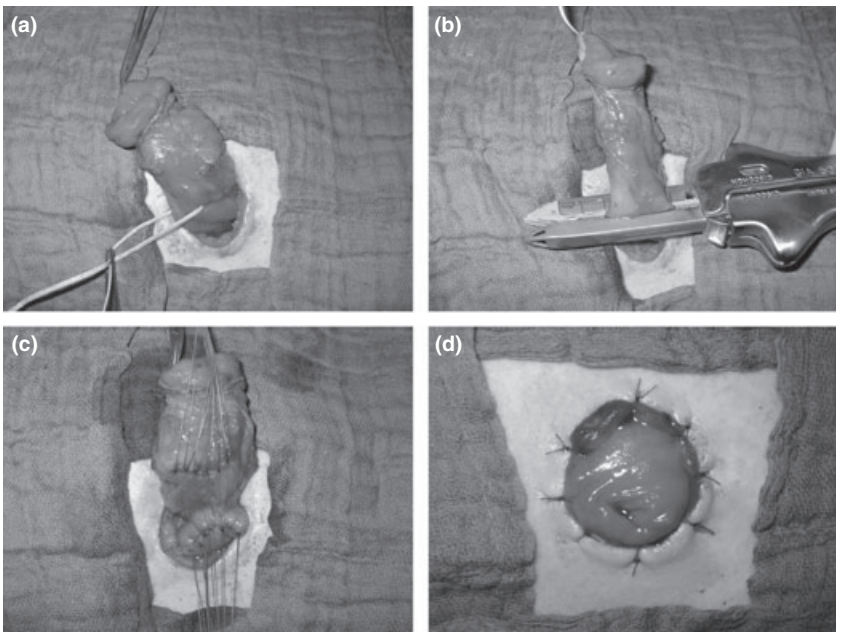

Figure 1 Technique of exclusion of terminal intestinal segment from gastrointestinal continuity after small bowel or multivisceral transplantation. (a) Isolation of the terminal intestinal segment from the ileostomy to the side-to-end intestinal (graft to patient's intestinum) anastomosis. (b) Disconnection of the gut with stapler device (GIA) maintaining the blood supply intact. (c) Both ends are oversewn with interrupted sutures. (d) Reinsertion of the excluded 'blind small bowel' segment in the abdominal wall.

Results

Patient and graft survival as well as complications are shown in Table 1. Graft endoscopy and forceps biopsies were performed on 280 occasions with 64 (23%) biopsies performed through the 'blind ostomy'. In total, 11 histologically proven acute allograft rejections between days 3 and 51 with two episodes in three cases were diagnosed. Endoscopic findings correlated well with the histologic severity of rejection. Acute rejection episodes were treated with bolus corticosteroids. One patient lost his graft because of ongoing treatment refractory exfoliative rejection. Another patient who received a combined intestinal and kidney transplantation was re-admitted after two rejection episodes on days 36 and 51, 4 months postoperatively with a small bowel obstruction without mucosal alterations of the graft. During explorative laparotomy severe, dense fibrous adhesions were found and the small bowel had to be removed. Histologic findings showed severe congestion and post-transplant lymphoproliferative disorder without signs of acute or chronic rejection. The patient died 2 months later with a functioning kidney graft because of multiorgan failure following pneumonia.

Five late mild acute rejections were diagnosed through the blind ostomy 3–37 months after transplantation. Histology revealed mild mononuclear infiltration of the

lamina propria and crypt destruction. Immunosuppression was intensified and endoscopy plus biopsy was repeated until normalization (Table 3).

Chronic rejection was observed in three (in one through the blind ostomy and in two patients with a permanent ileostomy) patients: four, 19 and 26 months after transplantation. In the case with the blind ostomy, repeated deep biopsies reaching the muscularis propria were performed. Two of these patients underwent isolated small bowel transplantation and at 26 and 36 months after the first transplantation were retransplanted with a multivisceral graft because of liver failure. Both patients are alive and doing well, one of them unfortunately with chronic renal insufficiency. The other patient experienced chronic rejection of the small bowel 4 months after multivisceral transplantation and was therefore retransplanted with an isolated small bowel allograft, but again developed chronic rejection 3 months later. She died of systemic nocardia infection 8 months after the first transplantation.

Typical CMV inclusions or equivocal inclusions with positive immunohistology were found in four patients, in one from the excluded enterostomy.

In three cases, simultaneous biopsies were taken from the excluded ostomy and the stomach in one and the small bowel via colonoscopy on two occasions. Whereas in one case a late acute rejection was diagnosed in the biopsies from the blind ostomy, results from the stomach were negative. In the second case, biopsies from the graft as well as from the excluded enterostomy indicate chronic rejection and the patient was ultimately retransplanted. Lastly, in another patient, protocol biopsies give a similar picture with normal mucosa and no signs of rejection.

A post-transplant lymphoproliferative disease (PTLD) was observed in two patients with normal functioning intestinal grafts, in one patient after a complicated postoperative course and two acute rejection episodes; she died 2 months after graft removal because of septic complications. In the other case, a 4-year-old girl with an uneventful postoperative course developed PTLD associated with an Epstein–Barr virus infection 2 months after transplantation. She died despite a significant decrease in immunosuppression, antiviral therapy, and anti-CD20 rituximab (Mabthera®; MabThera®, Roche, F. Hoffmann-La Roche AG, Basel, Switzerland).

Table 3. Rejection episodes in 20 patients after 24 intestinal transplantations and rejections diagnosed through the 'blind ostomy'.

Transplants (*n*)	24
Patients (*n*)	20
Blind ostomy (*n*)	9
Total rejection episodes (*n*)	19
Diagnosed through blind ostomy (*n*)	6
Late acute rejection (*n*)	5
Chronic rejection (*n*)	1

Discussion

The recent advance of powerful new immunosuppressive drugs has enabled long-term survival of small bowel allografts across strong immunogenetic barriers, and survival after intestinal and multivisceral transplantation has improved at the same time as the incidence and severity of rejections have declined. Although rejection *per se* is not the most common cause of death, patient death is frequently the final event in a cascade of events that start with under- or overestimation of rejection. Although acute rejection episodes can be successfully controlled, chronic rejection processes are still the predominant cause of graft loss. Prolonged allograft survival therefore needs close noninvasive monitoring to ensure timely treatment, on the one hand, and to avoid over-immunosuppression on the other hand. Only one of the patients with acute rejection lost the intestinal graft because of severe exfoliative rejection. In contrast, all patients with chronic rejection were retransplanted, of whom one died of recurrent chronic rejection and systemic nocardia infection. Mild late acute rejections, diagnosed in five instances through the blind stoma, were reversed by intensifying maintenance immunosuppression.

Histology is the standard for rejection diagnosis. Because rejection often starts as a spotty or patchy process, the result can be misjudged by random biopsy of the allograft mucosa, and in 40% of cases the findings are false-negative [17]. Biopsies taken even from macroscopically normal mucosa are therefore essential. Chronic rejection results in chronic ischemic damage with subsequent atrophy of the mucosa, progressive inflammation and diffuse sclerosing mesenteritis combined with shrinking of the intestinal wall leading to successive loss of graft function [9,12,18]. It affects approximately 8% of grafts [19] and occurs insidiously, resulting in late diagnosis. Diagnosis is based on mucosal architecture, IEL, epithelial apoptosis and the number of ganglion cells of the plexus myentericus.

Goulet *et al.* [20] reported that an intestinal allograft had to be removed from a child 17 months after transplantation because of chronic rejection with obliterative vasculopathy and corresponding muscular fibrosis but normal overlying mucosa. Once more, it is quite possible that the regenerative ability of the mucosa masks the features of a slow rejection process directed against the mucosa and preserves mucosal morphology and function [21]. It is evident that rejection of intestinal grafts is not associated with uniformly, but rather with variably intense histopathologic changes in mucosa and that

mucosal biopsies can be misleading in the severity of rejection. However, full-thickness cross-sections show allografts to be histologically quite uniform and intestinal grafts undergo a defined and predictable sequence of histologic changes, which allow sensitive and specific assessment of the status of intestinal allograft rejection [10]. The excluded enterostomy offers a long-term minimally invasive tool for allograft surveillance allowing deep biopsies including the submucosa reaching the muscularis propria and ensuring better histologic classification of the appropriate phases of immunologic graft injury. Through the 'blind ostomy,' five late mild acute rejections and one chronic rejection were diagnosed. In another patient, CMV enteritis was found by histology and confirmed by pp65 positivity.

Endoscopy *per se* plays an important role in the assessment of small bowel grafts. In 1999, Kato *et al.* [22] reported the first use of a zoom videoendoscope to evaluate graft bowel mucosa. As rejections show great anatomic variability, specimens should be taken at multiple sites [19]. Nevertheless, despite the use of a magnifying endoscope, protocol biopsies have to be taken by an experienced team. This procedure supplements the pathologic findings by visualizing a large intestinal surface in detail and enabling treatment of rejection to be initiated even before the histologic diagnosis is available. Furthermore, it allows treatment control of rejection [3]. In cases with signs of rejection, maintenance immunosuppression was intensified and endoscopy and biopsies repeated until the histologic signs of rejection disappeared. Also, after modifying the ostomy to form the blind-ending enterostomy, endoscopy can be easily performed. On the other hand, this technique makes it possible to perform biopsies independently of an endoscopic unit. Material can then be sent to the transplant center for histologic examination.

As chronic rejection and infection are the main limitations on survival after small bowel transplantation, exact and consequent graft monitoring over a long period of time remains one of the most important factors in preserving graft function and improving patient survival. Biopsies through the excluded cutaneous enterostomy offer as a first step easy access, prompt and accurate diagnosis of graft dysfunction and guarantee successful management of patients in the long-term follow-up after small bowel and multivisceral transplantation.

Authorship

AK designed the study, performed endoscopy and wrote the paper. RL, CI, WS, RÖ collected the data. FO, AK analyzed the histology. RM made an important contribution to finalize the paper.

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