Atlas of Enteroscopy

Editors

F.P. Rossini • G. Gay

Springer

1998

Enteroscopy of the transplanted small bowel

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Introduction

The general term "intestinal/multivisceral transplantation" (InMvTx) refers to an heterogeneous class of transplants involving the whole small bowel (jejunum+ ileum), transplanted "en bloc" and simultaneously with or without one or more segments of the upper or lower gastrointestinal tract ("visceral component": stomach, duodenum, colon) and with or without one or more solid abdominal organs ("solid organ component": liver, pancreas, sometimes kidney/s).

The visceral and solid organ components of the intestinal/multivisceral graft may be transplanted in different combinations (Fig. 1), as required by the single recipient candidates:

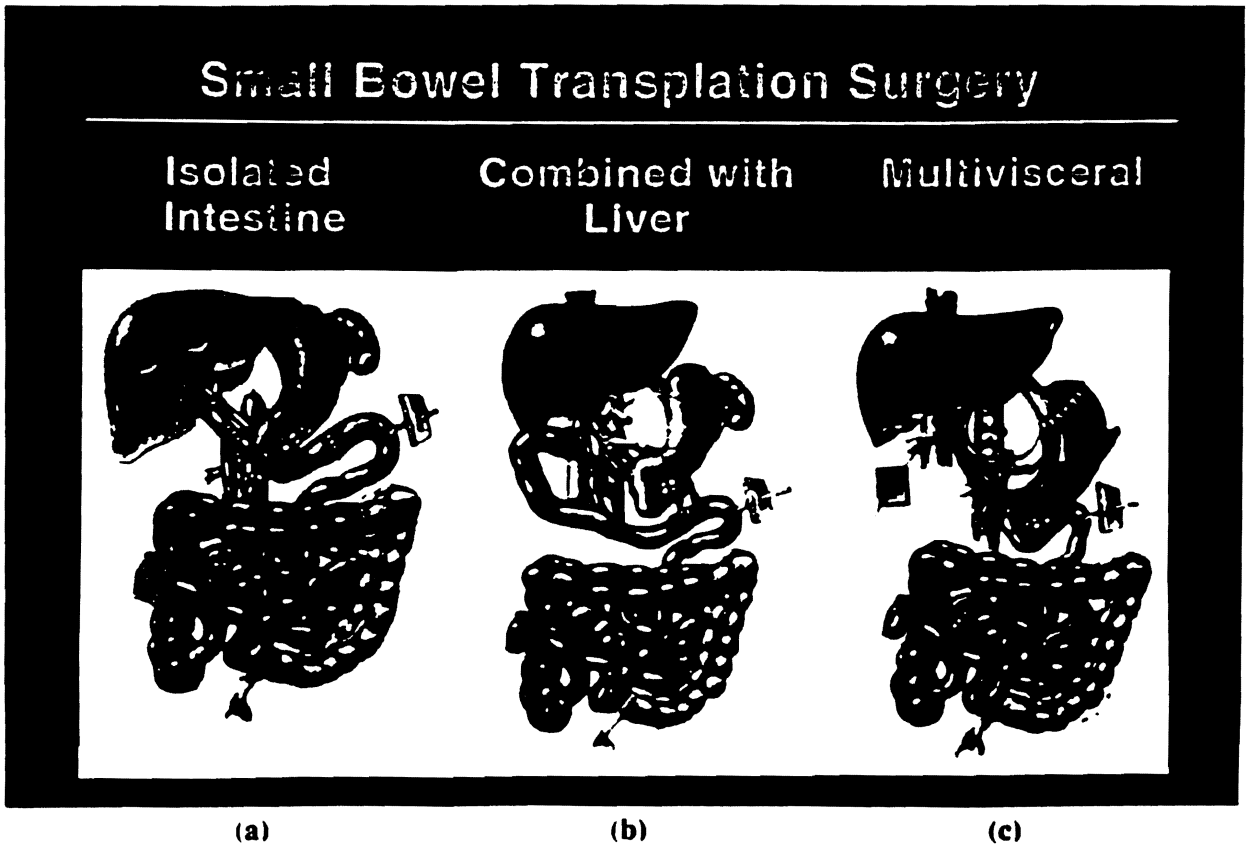


Fig. 1 a-c. The three different surgical types of intestinal and multivisceral transplanation: (a) isolated intestinal transplantation (iInTx); (b) combined liver and intestine transplantation (cLvInTx); (c) multivisceral transplantation (MvTx)

- Isolated intestine transplantation (iInTx):
  - Small bowel (SBTx)
  - Small bowel + colon (InTx)
- Combined liver and intestine tranplantation (cLvInTx):
  - Liver + small bowel (LvSBTx)
  - Liver + small bowel + colon (LvInTx)
- Multivisceral transplantation (MvTx):
  - Stomach + duodenum + liver + pancreas + intestine + (kidney/s)

Intestinal/multivisceral transplantation is usually indicated as a radical ultimate therapeutic option in the following two general clinical situations:

- for patients with chronic, irreversible end-stage intestinal failure, as an alternative and definitive treatment to unfeasible long-term TPN (relapsing TPN-induced complications: frequent line-related sepsis, extensive central vein thrombosis, exhaustion of the central venous access sites for TPN cannulation);
- for patients with otherwise normal intestine, but requiring simultaneous intestinal transplantation as an absolutely complementary surgical step, needed to replace different failed life-saving intra-abdominal solid organs (liver, pancreas).

More specifically, the indications for the different types of InMvTx (iInTx vs cLnInTx vs MvTx), as well as the various allograft organ configurations, rely on the anatomical integrity and on the functional status of the residual segments of the native gastrointestinal tract and of the native intra-abdominal solid organs (liver, pancreas). Such specific indications are summarized in Table 1.

Although attempted more than three decades ago, intestinal grafts have been considered until recently "forbidden organs" because of the high frequency of technical, immunological and infectious complications. It has been only since the advent of more refined harvesting and preservation procedures, of improved surgical techniques, of more effective immunosuppression (tacrolimus, mycophenolate/mofetil), and more sophisticated intra- and post-operative monitoring and treatment protocols that intestinal and multivisceral transplantation has become a clinical reality. However, the optimal management of InMvTx recipients still remains difficult and disputable, and major immunological or infectious complications still continue to pose threatening problems.

The post-operative course of InMvTx recipients is usually problematic and complicated, mainly in those patients who pre-operatively presented with severe deterioration of their physical performance status and with various organ system failures, which can persist and endure post-operatively even in the face of satisfactory allograft function. The post-operative course is usually more troubled in cLvInTx and in MvTx than in iInTx patients, who generally present a lesser medical acuity.

Consequently, post-operative monitoring and management of these patients require a very aggressive and multidisciplinary approach by the nursing and medical staff (surgeons, anesthesiologists, CCM physicians, internal medicine specialists, gastroenterologists and endoscopists, radiologists, pathologists).

It also requires easy availability and access to diagnostic facilities (immunologic and infectious surveillance, sophisticated hemodynamic monitoring, bronchoscopy, TEGraphy, non-invasive and invasive radiology, histopathology, emergency laboratory tests), as well as timely and prompt therapeutic modalities (immunosuppressive and immunodulation management, antibiotic therapy, mechanical ventilation and respiratory treatment, hemodialysis, fluid and nutritional support, emergency surgery for complications, etc.).

Most important, however, is a continuous, dedicated, diligent commitment to patient surveillance and care by medical, surgical and nursing personnel: any subjective symptom or complaint, as well as any new objective physical sign or change in the patient's clinical picture (Table 2 A, B), must be aggressively pursued and carefully investigated until the cause is found or it resolves.

Although sometimes difficult to achieve, early diagnosis of post-operative complications is a major determinant in successful InMvTx, being a "conditio sine qua non" for immediate, specific, effective therapy. Post-operative monitoring of InMvTx recipients is addressed to detect as early as possible the onset of post-transplant complications, mainly immunological and infectious, as well as to assess the intestinal graft's anatomic and functional integrity

Table 1. Indications for intestinal/multivisceral transplantation

TRANSPLANTATION TYPE	INDICATIONS
ISOLATED INTESTINAL TRANSPLANTATION (iInTx)	1) **SURGICAL "SHORT GUT SYNDROME"** (loss ≥ 80%): a) **in adult patients:** • abdominal trauma • vascular diseases involving the CA[1] and/or the SMA[2] • multiple extensive intestinal resections for surgical adhesions from previous surgeries • Crohn's disease • Gardner's syndrome • incarcerating intra-abdominal desmoid tumors b) **in pediatric patients:** • intestinal atresia • gastroschisis • mid-gut volvulus • necrotizing enterocolitis 2) **CHRONIC PSEUDO-OBSTRUCTION SYNDROMES:** from • visceral myopathy • visceral neuropathy • total intestinal aganglionosis 3) **SEVERE ENTEROCYTE ABSORTIVE/SECRETORY DYSFUNCTION:** from • microvillous inclusion disease • radiation enteritis • diffuse inflammatory bowel disease • massive intestinal polyposis syndromes • protein-losing enteropathy
COMBINED HEPATIC/INTESTINAL TRANSPLANTATION (cLvInTx)	1) **COEXISTENT INTESTINAL & HEPATIC FAILURE:** from • short gut syndrome + • long-term TPN[3]-induced end-stage liver disease 2) **OLTx[4] CANDIDATES WITH CONCOMITANT EXTENSIVE THROMBOSIS OF THE ENTIRE PORTOMESENTERIC VENOUS SYSTEM** (requiring total enterectomy of otherwise normally functioning intestine)
MULTIVISCERAL TRANSPLANTATION (MvTx)	1) **COEXISTENT TERMINAL INTESTINAL, HEPATIC, PANCREATIC DISEASE:** from extensive thrombosis of the splanchnic and/or inferior vena cava systems, due to • congenital protein C deficiency • congenital protein S deficiency • congenital anti-thrombin III deficiency 2) **LOW-MALIGNANT DIFFUSE INTRA-ABDOMINAL TUMORS:** • diffuse polyposis syndromes • desmoid tumors 3) **POTENTIALLY CURABLE MALIGNANCIES:** requiring upper abdominal exenteration • gastrinoma • carcinoid 4) **SEVERE GI MOTILITY DISORDERS:** • myogenic pseudo-obstruction syndrome • neurogenic pseudo-obstruction syndrome

[1]CA: celiac axis; [2]SMA: superior mesenteric artery; [3]TPN: total parenteral nutrition; [4]OLTx: orthotopic liver transplantation

Table 2. Pre-endoscopic and endoscopic findings in intestinal/multivisceral transplantation

A. PRE-ENDOSCOPIC SYMPTOMS	B. PRE-ENDOSCOPIC PHYSICAL SIGNS	C. ENDOSCOPIC FINDINGS & DESCRIPTIVE ENDOSCOPIC VOCABULARY
• fever • chills • weight loss • mood changes • abdominal distension • abdominal pain • anorexia • dysphagia • odynophagia • regurgitation • heartburn • nausea • vomiting • constipation • diarrhea • intestinal bleeding • melena • hematochezia	• fever • sepsis, septic shock • ARDS-like syndrome • toxemia • malnutrition • dehydration • weight loss • abdominal distension • abdominal tenderness • abdominal muscular spasticity/rigidity • stomal appearance • high stomal output • diarrhea • intestinal bleeding - occult - melena - hematochezia • alterations in bowel movement habits: - obstipation/constipation - obstruction - paralytic ileus	• mucosal findings & distribution (punctate, spotty, patchy, segmental, diffuse): - velvety, glistening appearance - erythema - hyperemia - apparent vascularity - edema - pale, ischemic appearance - congested, dusky, cyanotic appearance - granularity - nodularity - friability - sloughing of the mucosa - erosion - ulcer - exudate - pseudomembrane - thickening of the mucosa - flattening or atrophy of the mucosal folds - stiffness and tubular appearance of the loop • luminal content: - feces consistency and appearance - stomal output - increased - decreased - loose stools - watery diarrhea - intestinal bleeding, melena, hematochezia • intestinal loop motility: - hypoperistalsis, hypokinesis - paralytic ileus - hyperperistalsis

(absorption, motility, fluid and electrolyte balance, nutritional status).

Unlike heart, kidney, pancreas and liver transplantation, the intestine (as well as the lung), is the only organ which can be endoscopically explored and monitored after transplantation for major immunological (acute cellular rejection, chronic rejection, graft-versus-host disease) or infectious complications (CMV enteritis, EBV infection with PTLD, mycotic enteritis). While the diagnosis of infection is relatively easy and clear-cut, monitoring of the intestinal graft for immunological complications (mainly acute cellular rejection) is difficult and disputable because there are no clearly defined specific clinical and laboratory parameters known to be reliable and of value. Consequently, enteroscopy, endoscopy-guided biopsies, endoscopic medication and surgery of the graft can play a critical role and be, together with histopathology, the cornerstone of post-operative monitoring and management of intestinal/multivisceral transplant recipients.

Enteroscopy methodologies and procedures in intestinal/multivisceral transplantation recipients

Indications for intestinal graft enteroscopy

The indications for enteroscopic evaluation include routine surveillance (25%) or the onset of pre-endoscopic clinical symptoms (Table 2 A) or pre-endoscopic physical signs (Table 2 B) (75%), consistent with the initial outbreak of major complications.

More accurately, the most frequent clinical indications for intestinal graft endoscopy in

adult InMvTx recipients are: abdominal pain (72%), increased stomal output (46%), abdominal distension (30%), nausea (20%), fever (17%), vomiting (10%), intestinal bleeding (10%) and sepsis (4%).

In pediatric InMvTx patients, the most frequent indications for the enteroscopies are: fever, change in stomal output and appearance, gastro-intestinal bleeding and others (sepsis, skin rash, etc.).

Enteroscopic procedures

The enteroscopic procedures performed in recipients of intestinal/multivisceral transplants differ in some aspects from the standard methodologies and protocols utilized in non-transplanted patients.

Because of the frequent patchy or segmental topographic anatomic distribution of the immunological and/or infectious lesions in the mucosa of the different intestinal segments of the transplanted graft (stomach, duodenum, jejunum, ileum, colon), the enteroscopic procedure should explore as much gastrointestinal tract as possible in order to avoid "skip" lesions and minimize underevaluation of the initial and ongoing complications.

Enteroscopies are usually performed mainly by trans-stomal terminal ileoscopy or trans-stomal ileocolonoscopy(63%), but also by trans-stomal jejunoscopy (4%), esophagogastroduodenoscopy (23%), and lower proctosigmoid colonoscopy (10%).

Routine surveillance enteroscopies are done twice a week for the 1st month, once a week for the next 2 months, monthly for the next 3 months and every 3-6 months thereafter.

In addition, whenever the evolving clinical picture of the InMvTx recipients (Table 2 A, B) is consistent with the onset of major complications, timely turning to gastroenteroscopy is absolutely mandatory.

Because data which define the endoscopic appearance of the intestinal graft or that correlate the symptoms and signs of rejection and/or infection with concurrent graft endoscopic appearance are still lacking or inadequately outlined, a standardized enteroscopic descriptive vocabulary referring to endoscopic features found in transplanted intestinal grafts complicated by immunological or infectious events has been developed and presented herein (Table 2 C). The aim of this standardized enteroscopic descriptive vocabulary is to accomplish easily identifiable features and terms with a high degree of reproducibility, as well as to minimize the examiner variations, thus increasing the value and reliability of the overall endoscopic examination as a diagnostic tool for intestinal and multivisceral graft complications.

The endoscopic procedures performed in patients with intestinal and multivisceral transplantation should be frequently captured and saved on videotape to generate an enteroscopic video-library, thus allowing the comparative assessment of previous and subsequent enteroscopic features, as well as the endoscopic evaluation of the clinical course of the intestinal/multivisceral transplant.

Since the histopathologic diagnosis is still considered the gold standard for comparison, enteroscopic evaluation should not be used as the sole and exclusive tool in diagnosing immunological and infectious complications; consequently, enteroscopy must be routinely associated with multiple, selective, endoscopy-guided mucosal biopsies.

Monitoring of immunological and infectious complications in human clinical intestinal and multivisceral transplantation

In monitoring post-operative immunological and infectious complications in intestinal and multivisceral transplantation recipients, the indication to enteroscopic evaluation is based mainly on clinical criteria (Table 2 A, B). Furthermore, the sensitivity, specificity, positive or negative predictive value and diagnostic accuracy of using the endoscopic findings (Table 2 C) as predictors of the immunological or infectious complications in the intestinal/multivisceral graft have yet to be fully established. As a matter of fact, complete endoscopic surveillance of all gastroenteric segments of the transplanted graft for diagnostic purpose or for biopsy sampling is not always feasible or safe. Additionally, in the intestinal graft acute cellular rejection lesions are unevenly distributed in a spotty or segmen-

tal fashion, often ileal-centered, thus making endoscopy problematic and unsafe to be performed. Moreover, several frequent endoscopic findings (edema, erythema, erosions, ulcers) are not specific, being found both in immunological (ACR) and in infectious (CMV enteritis) complications. Consequently, because of these methodological limitations, enteroscopy should not be the sole unique diagnostic tool, but it has to be always compared with an available reference gold standard, ideally represented by the histopathologic examination. In the clinical setting, histopathology may be not always available, so the following alternative diagnostic options should be used, such as comparison and correlation of enteroscopic and histopathological findings with clinical assessment and outcome, as well as with imaging criteria.

Clinical findings

Clinical monitoring of the intestinal graft is accomplished by multiple daily clinical evaluations, focusing on the patient's general clinical status and on the patterns of the intestinal stoma (Table 2 A,B).

Acute intestinal allograft rejection

Acute intestinal allograft rejection (Fig. 2) may be asymptomatic, but usually presents an array of symptoms and physical signs (Table 2 A, B), including fever, weakness, mood changes, abdominal pain, abdominal distension, hypoperistalsis and paralytic ileus, nausea and vomiting, diarrhea or sudden increase of watery stomal discharge.

The intestinal graft stoma (usually an ileostomy) is carefully examined for color, texture and friability of the mucosa; the stoma may progressively become edematous, erythematous, pale, congested, dusky and friable.

Stomal output is assessed for volume, consistency, presence of blood and of reducing substances, tested by pH and clinitest, and reflecting, besides rejection, also infection and malab-

Fig. 2. Gross appearance of early acute cellular rejection in an isolated small bowel allograft: the recipient has been surgically explored because of fever, sepsis, ARDS-like syndrome, abdominal pain, abdominal distension, hypoperistalsis and increase of watery stomal discharge. The intestinal loops look erythematous, edematous, slightly distended, hypokynetic

sorption. In more severe episodes of acute graft rejection, erosions, ulcerations and sloughing of the intestinal mucosa may occur, with gastrointestinal bleeding, graft paralytic ileus and decrease or absence of stomal discharge.

Due to disruption of the normal intestinal mucosal barrier, bacterial and/or fungal translocation can develop, with consequent sepsis, septic shock and/or ARDS-like syndromes.

Clinical criteria are the keystone for early diagnosis of acute rejection of the intestinal graft. Unlike rejection of other isolated solid organ allografts (heart, lung, liver, kidney, pancreas), whose diagnosis is mainly attained by biopsy and/or by functional or laboratory tests, diagnosis of intestinal acute rejection has to be primarily based on clinical criteria, which usually present first. In InMvTx endoscopic, bioptic, radiological and metabolic parameters of acute rejection often come too late: they help to confirm, not to make the primary diagnosis of acute rejection. It would be an unforgivable mistake and a waste of precious time if we were to wait too long for these results to start immunosuppressive treatment, since only a few hours may be available for effectively and safely reversing the ongoing immunological injury.

Chronic intestinal allograft rejection

Chronic rejection of intestinal allografts (Fig. 3) has been recorded in recipients with persistent or recurrent intractable acute rejection episodes. Clinical presentation consists of chronic progressive allograft dysfunction with intermittent fever, worsening malnutrition, weight loss, chronic long-lasting exacerbating abdominal pain, recurrent or persistent intractable diarrhea with dehydration, intermittent melena or enterorrhagia, relapsing septic episodes.

Fig. 3. Macroscopic aspect of an isolated intestinal allograft with chronic rejection: intraoperative picture before total graft enterectomy and retransplantation after 667 days since the primary iInTx. The recipient's clinical course consisted of recurrent acute rejection episodes, with progressive allograft dysfunction, relapsing septic episodes, intermittent fever, malnutrition, weight loss, exacerbating abdominal pain, refractory diarrhea with dehydration, melena. The intestinal loops show a rigid, stiff, tubular, hypokinetic appearance, with segmental strictures and dilations, along with ischemic areas and intestinal perforations

Graft-versus-host disease

The clinical picture of the infrequently occurring graft-versus-host disease episodes (5%) include fever, skin rash, septic-like syndrome, abdominal pain and distension, changes in the stomal appearance and output.

Infectious complications

Clinical presentation of infectious complications varies with the infectious etiologic pathogens. Bacterial infections clinically present mostly as line sepsis, pneumonia, wound and intra-abdominal abscesses.

Fungal infections occur in the esophagus, peritoneal cavity, paranasal sinuses, upper and lower respiratory system.

Viral infections present in adults mainly as CMV enteritis; other clinical pictures consist of CMV hepatitis, pneumonitis, gastritis, retinitis and diffuse CMV syndrome. Pediatric recipients seem more prone to EBV infections (PTLD and acute lymphadenitis), which should be suspected when clinical symptoms and signs including fever, abdominal pain, bleeding and /or vomiting occur. These features vary according to the location of the lesions, their size and the depth of mucosal invasion. PTLD can be further complicated by acute cellular rejection, owing to reduced immunosuppression required to treat the lymphoproliferative disease. Moreover, PTLD may be complicated by sepsis and toxemia, secondary to the entrance of the enteric flora and toxins through the disrupted mucosal barrier.

Exclusive infectious clinical and physiopathological features occurring in this unique

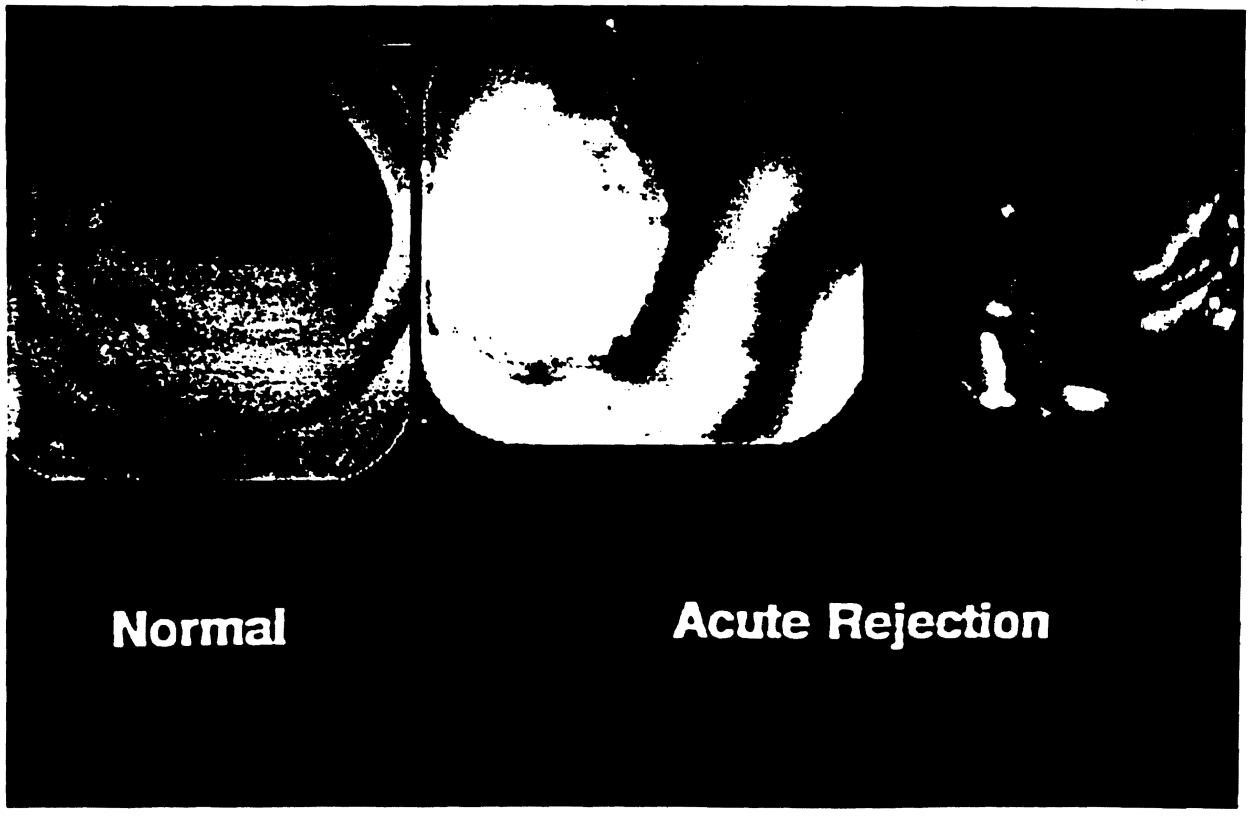


Fig. 4 a-c. Enteroscopic appearance of an isolated intestinal allograft with acute cellular rejection:(a) reference picture of a normal intestinal allograft (ileum); (b) early moderate acute cellular rejection: the mucosa is edematous, has lost its peculiar glistening and velvety appearance, is friable, with submucosal nodularity and small mucosal ulcers; (c) severe acute cellular rejection: the intestinal mucosa shows diffuse erosions with sloughing of extensive areas of its superficial layer, intestinal bleeding and paralytic ileus (by courtesy of Lippincot-Raven Publishers, Philadelphia, USA; from: Fung JJ, Abu-Elmagd K and Todo S: Intestinal and Multivisceral Transplantation. In: *Digestive Tract Surgery: a Text and Atlas*, Fig. 35.15, p. 1212)

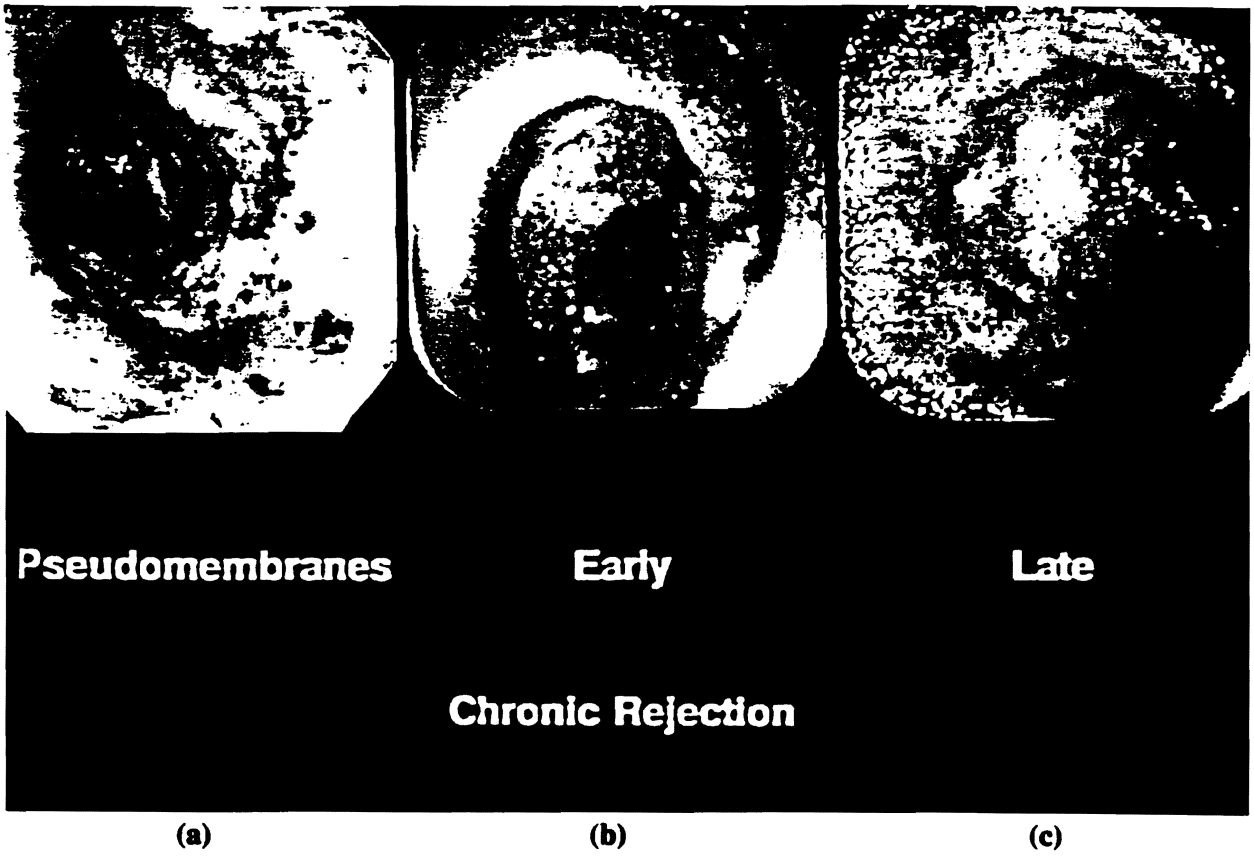


Fig. 5 a-c. Enteroscopic appearance of an isolated intestinal allograft with chronic rejection: (a) early chronic intestinal allograft rejection: the mucosa shows submucosal nodularity, focal erosions with development of pseudomembranes; (b) early chronic intestinal allograft rejection: hypokinetic appearance of the intestinal loop, with edema of the mucosa, flattening of the mucosal folds, fine mucosal granularity with submucosal nodularity and focal erosions; (c) late phase of severe chronic intestinal allograft rejection: rigid, tubular, akinetic appearance of the intestinal loop, with thickening of the mucosa, atrophy of the mucosal folds, chronic ulcerations with intestinal bleeding (by courtesy of Lippincot-Raven Publishers, Philadelphia, USA; from: Fung JJ, Abu-Elmagd K and Todo S: Intestinal and Multivisceral Transplantation. In: *Digestive Tract Surgery: a Text and Atlas*, Fig. 35.117, p. 1243)

patient population are microbial overgrowth and translocation.

In addition to daily infectious surveillance tests routinely performed in any transplant patient, infection monitoring of InMvTx recipients should include frequent cultures of the blood, sputum, bronchial and alveolar secretions, urine, surgical wound exudate and drains' fluid. Most important are quantitative cultures of the stools and of the stomal discharge in order to monitor significant changes in the intestinal microflora and to confirm direct correlation between the onset of systemic infectious episodes and the simultaneously ongoing microbial overgrowth and translocation processes.

In all cases of sepsis of unexplained origin in any InMvTx recipient, the basic general principle of endoscopically and radiologically exploring each of the surgical anastomoses (gastrointestinal, biliary, vascular) by different enteroscopic procedures and by ultrasound, Doppler sonography, CT scan, angiography, barium contrast series, PTC, etc. is paramount and should always be promptly considered and timely performed.

Endoscopic findings

Acute intestinal allograft rejection

Endoscopic features of mild-to-moderate acute intestinal graft rejection are edema of the mucosa, which can progressively become focally or diffusely erythematous, hyperemic, con-

gested and dusky. It can lose its fine, glistening and velvety appearance and become hypoperistaltic, friable, with fine mucosal granularity and focal erosions (Fig. 4b). More severe rejection presents with submucosal nodularity, focal or diffuse ulcerations, sloughing of extensive areas of the mucosa with development of pseudomembranes, intestinal bleeding and absence of peristalsis (Fig. 4c).

Chronic intestinal allograft rejection

Chronic intestinal allograft rejection in its early course can show features similar to those enteroscopically found in late ongoing or relapsing acute cellular rejection of the intestinal allograft (Fig. 5b).

Endoscopic examination of late chronic intestinal allograft rejection shows a rigid, stiff, tubular, hypokinetic appearance of the intestinal loops, with thickening of the mucosa, flattening or atrophy of the mucosal folds, chronic ulcerations with pseudomembranes and intestinal bleeding (Fig. 5c).

Infectious complications

Differential endoscopic diagnosis should be made between acute cellular rejection of the intestinal graft and CMV enteritis occurring mostly in adult recipients, and intestinal PTLD presenting mainly in pediatric patients.

The endoscopic features of CMV enteritis include punctuate areas of erythema, spotty mucosal erosions and focal ulcerations (Fig. 6a).

Fungal enteritis endoscopically shows superficial, white, curdy patches, sometimes growing together into large, soft and light membranes. These are easily removed, leaving an erythema-

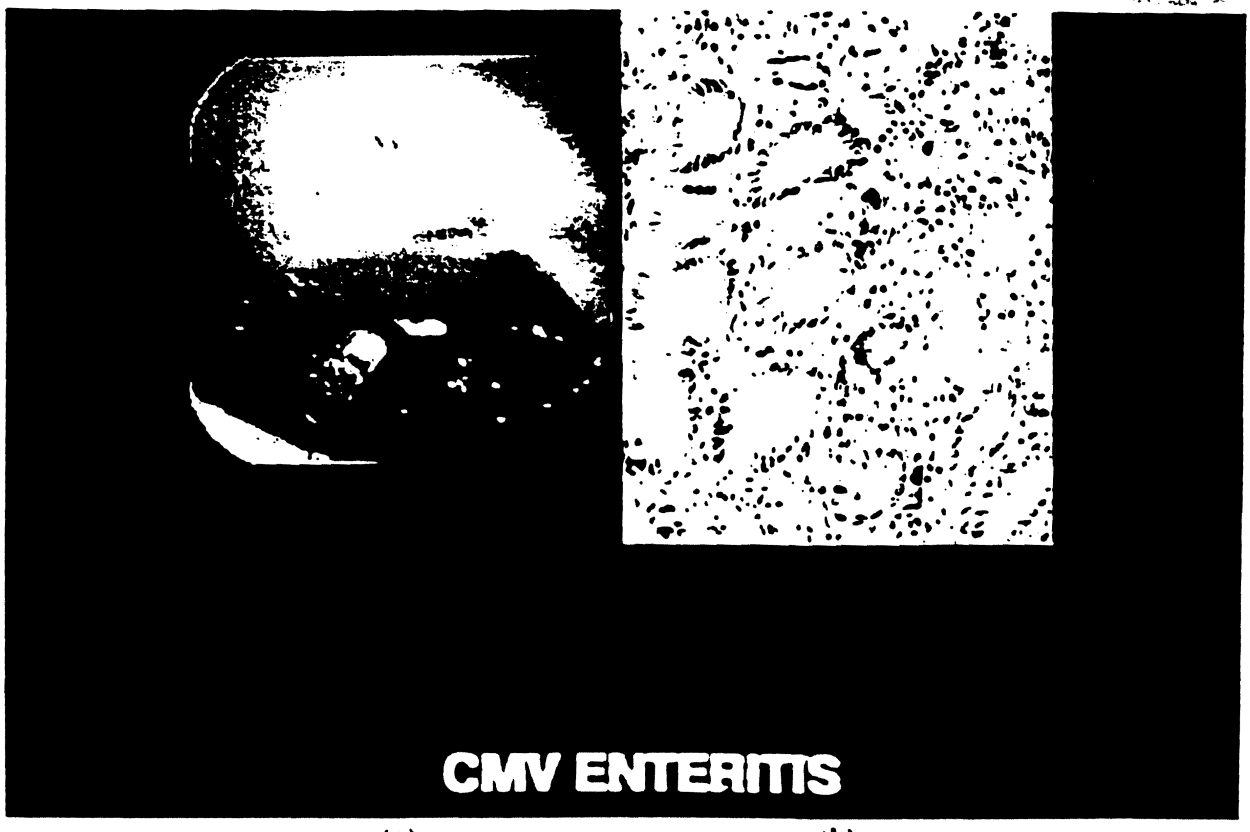


Fig. 6 a,b. Cytomegalovirus enteritis in an intestinal allograft: (a) endoscopic picture: the mucosa shows edema, punctate areas of erythema and focal mucosal erosion; (b) histopathologic picture: giant mucosal epithelial cells, with pleomorphic nuclei, basophilic nuclear and cytoplasmic inclusion bodies, mixed inflammatory cell infiltrate, cryptitis

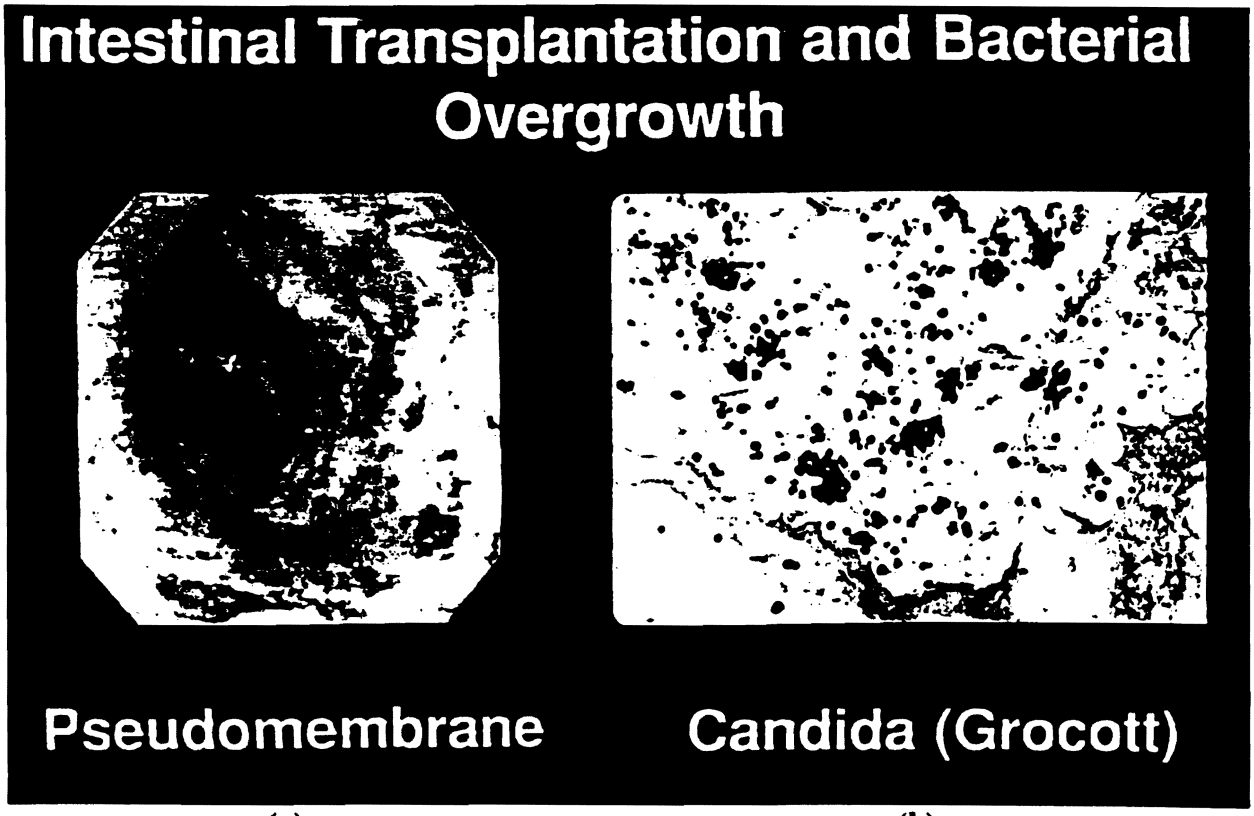


Fig. 7 a,b. *Candida albicans* enteritis in an intestinal allograft: (a) endoscopic picture: superficial, white, curdy patches growing into light pseudomembranes, with erythematous, inflamed surrounding and underlying mucosa; (b) histopathologic picture: yeasts and pseudohyphae within the pseudomembrane and the underlying mucosal epithelial layer

Table 3. Histopathological findings in InMvTx immunological complications

ACUTE CELLULAR REJECTION	CHRONIC REJECTION
a) **early, mild to moderate ACR:** • widening of the lamina propria • edema • mixed inflammatory mononuclear infiltrate (large activated lymphoblasts, small lymphocytes, macrophages, plasma cells, eosinophils, neutrophil granulocytes, • focal endothelialitis • infiltration of the basal membrane and of the epithelium • cryptitis with apoptosis • goblet and Paneth cell depletion • epithelial cell necrosis • crypt loss b) **late, advanced, severe ACR:** • mucosal sloughing • focal ulcerations • crypt destruction • neutrophil plugging of capillaries • granulation tissue • inflammatory pseudomembranes c) **healing and regeneration changes:** • architecture disruption • doubling of the epithelial monolayer • distorted, uneven cryptic lumen • villous blunting	a) **early, moderate chronic rejection:** • progressive distortion of the mucosal architecture • villous blunting • widening of the lamina propria • scant cellular infiltrate • severe prominent cryptitis • cryptic cell apoptosis • depletion or loss of goblet and Paneth cells b) **advanced, severe chronic rejection:** • focal chronic ulcerations • mucosal microabscesses • epithelial metaplasia • fibrosis of the lamina propria • fibrosis of the submucosa • fibrosis of the mesenteric lymph nodes • obliterative arteriopathy of the intestinal arterioles

tous, irritated, inflamed underlying mucosal surface (Fig. 7a).

Endoscopically, PTLD early lesions are not specific, consisting of non-ulcerated nodules of the submucosa, covered by the overlying mucosal layer with or without concurrent erythema. In contrast, well-developed PTLD lesions are peculiar, represented by submucosal nodules up to 2 cm in diameter, with deep necrotic central areas surrounded by heaped-up mucosa.

Histopathological findings

Histopathological criteria (Table 3) are the gold standard reference, with which clinical, enteroscopic and radiological findings should be compared. Specific histological criteria for acute cellular rejection (mild, moderate, severe), chronic rejection (early, late), based on extension of inflammatory infiltrate, severity of crypt cell damage and apoptosis, focal or diffuse ulceration, severity of intestinal mucosal architecture

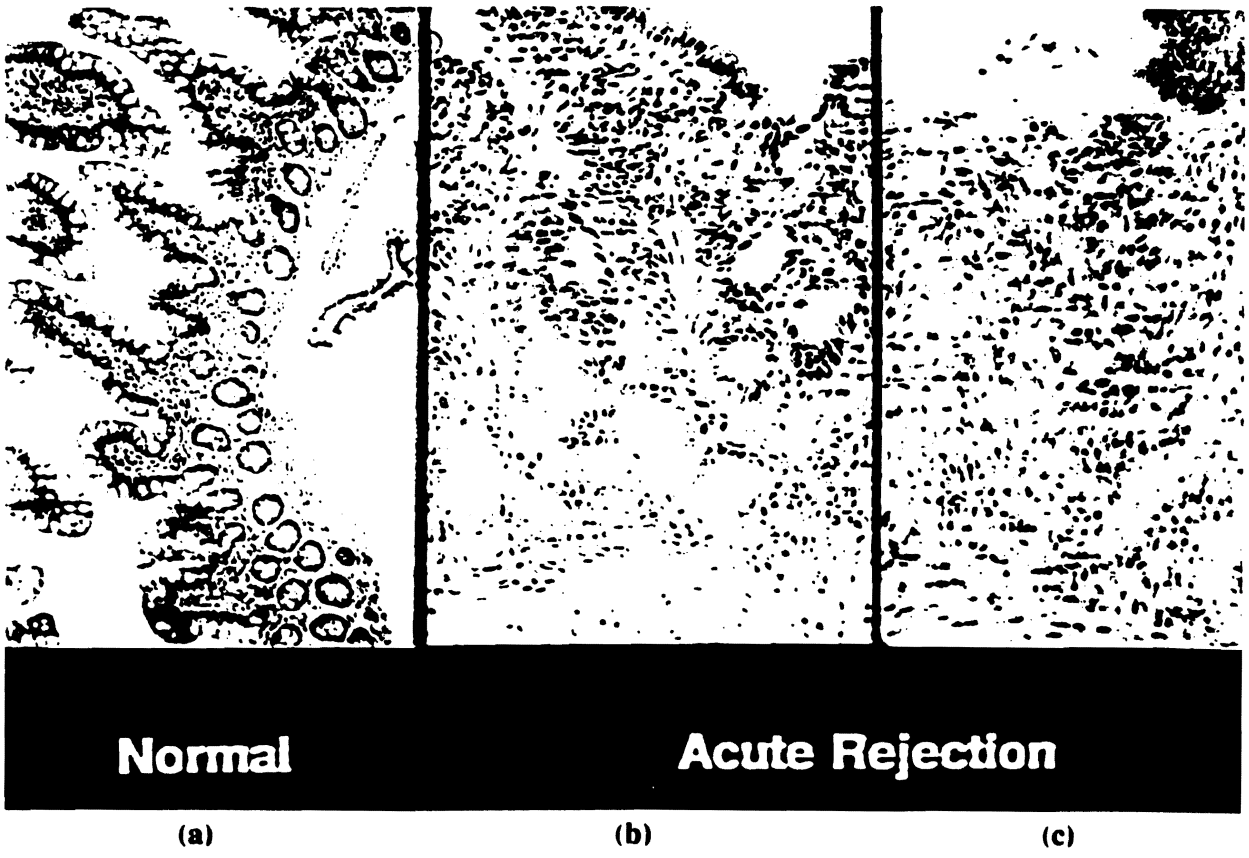


Fig. 8 a-c. Histopathology of intestinal allograft acute cellular rejection: (a) reference picture of a normal intestinal allograft; (b) early mild acute cellular rejection: the major histopathological patterns include widening of the lamina propria, with edema, mononuclear cellular infiltrate, capillary congestion with endothelialitis, significant crypt damage (cryptitis) with infiltration of the basal membrane and of the mucosal epithelial layer, depletion of goblet and Paneth cells, epithelial cell necrosis; (c) advanced and severe uncontrolled acute cellular rejection: the endoscopy-guided superficial biopsy shows a thick, mixed pleomorphic inflammatory infiltrate of the lamina propria and submucosa, massive crypt loss, blunting of the villi, mucosal sloughing with pseudomembranes and widespread mucosal destruction. The cellular infiltrate components are mainly large activated lymphoblasts and small lymphocytes, along with macrophages, plasmacells, eosinophils and sometimes neutrophil granulocytes (by courtesy of Lippincot-Raven Publishers, Philadelphia, USA; from: Fung JJ, Abu-Elmagd K and Todo S: Intestinal and Multivisceral Transplantation. In: *Digestive Tract Surgery: a Text and Atlas*, Fig. 35.116, p. 1243)

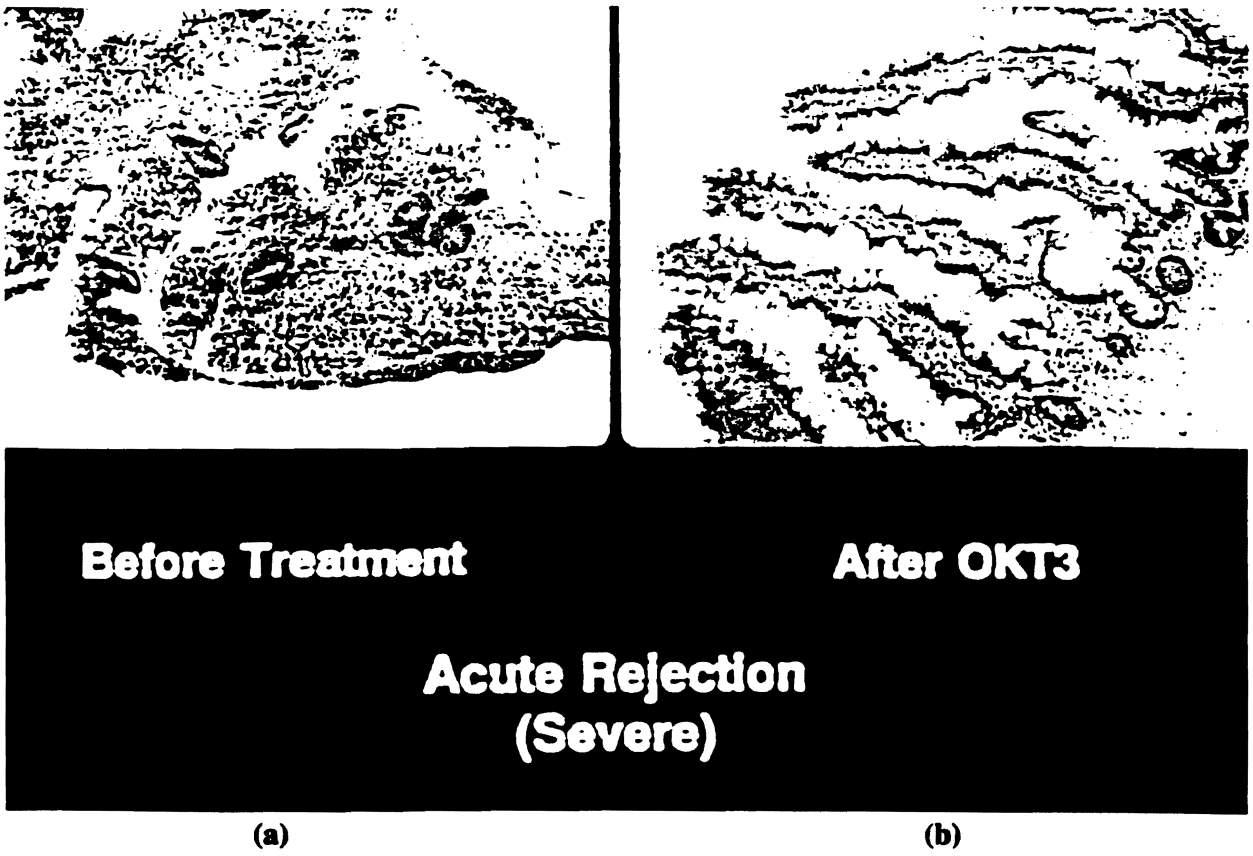


Fig. 9 a,b. Histopathology of intestinal allograft acute cellular rejection: (a) ongoing severe acute cellular rejection before treatment: the histological picture includes mixed pleomorphic inflammatory infiltrate of the lamina propria, cryptitis and crypt loss, complete mucosal sloughing with focal ulceration and replacing granulation tissue and pseudomembranes, disruption of the normal enteric mucosal architecture; (b) after timely, aggressive and successful treatment of the ongoing acute cellular rejection episode, owing to the peculiar regenerative capacities of the enteric mucosa, it can revert to an almost normal histological structure. Histological healing comes late, usually 5-7 days after the clinically improving response

distortion, as well as for graft-versus-host disease and infectious lesions (namely, CMV and EBV injuries) in the transplanted intestinal allograft, are now available with adequate accuracy.

Acute intestinal allograft rejection

In mild to moderate rejection (Fig. 8), histopathological criteria consist of widening of the lamina propria, with edema, mixed inflammatory mononuclear infiltrate and focal endothelialitis (inflammatory cells adherent to or infiltrating the injured endothelium).

The cellular infiltrate components are mainly activated lymphoblasts and small lymphocytes, along with macrophages, plasma cells, eosinophils and sometimes neutrophil granulocytes.

The cellular infiltrate can traverse the muscularis mucosae as well as invade the basal membrane, with resultant infiltration of the mucosal epithelial layer.

Cryptitis with apoptosis, goblet and Paneth cell depletion, epithelial cell necrosis and final crypt loss of various degrees are further histologic findings of mild to moderate acute intestinal rejection.

At a more advanced and severe stage (Fig. 9), complete mucosal sloughing, focal ulcerations, crypt destruction, neutrophil plugging of capillaries, replacing granulation tissue and inflammatory pseudomembranes are found.

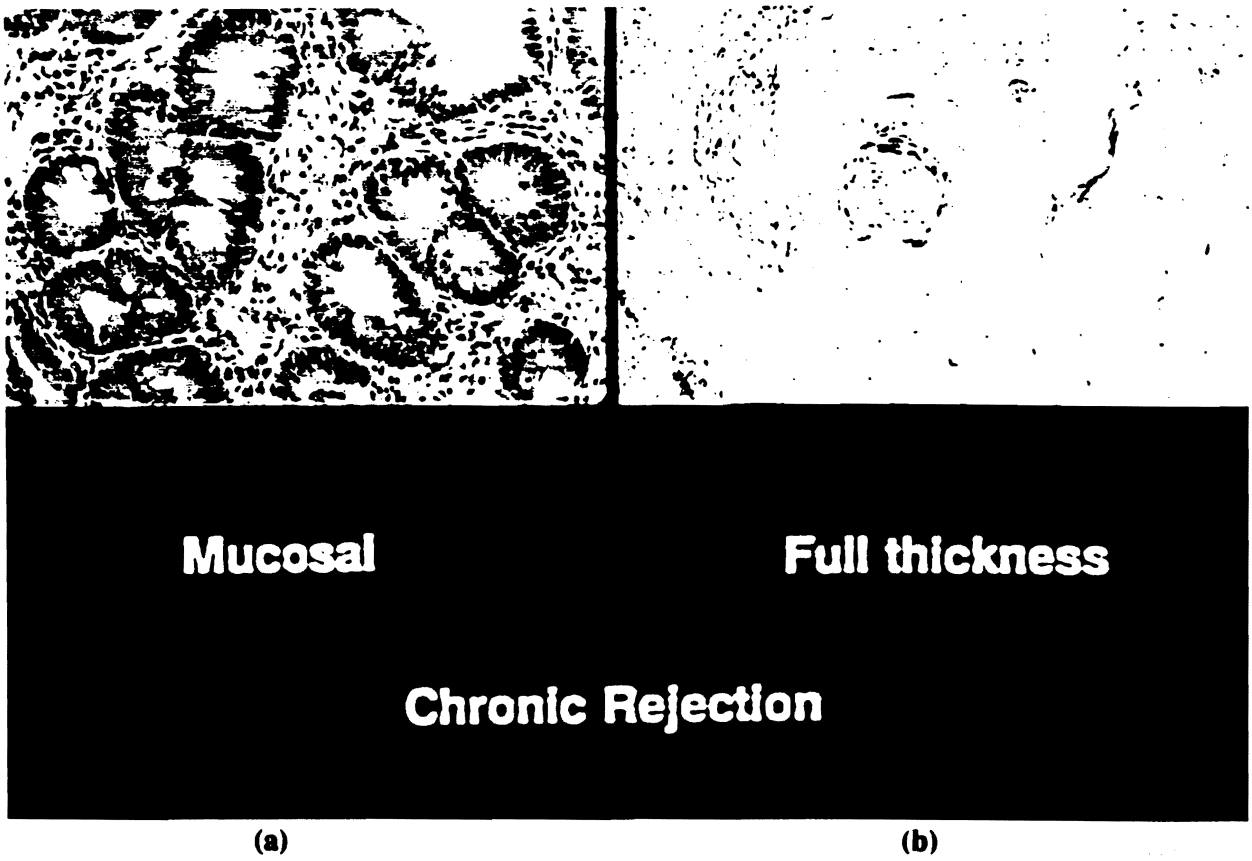


Fig. 10 a,b. Histopathology of intestinal allograft chronic rejection: (a) endoscopic-guided superficial mucosal biopsy includes progressive distortion of the mucosal architecture, villous blunting, widening and fibrosis of the lamina propria with scan cellular infiltrate, prominent cryptitis with crypt loss; (b) full-thickness intestinal biopsy shows chronic obliterative arteriopathy of the intestinal arterioles

Healing and regeneration changes occur, overlapping the above histopathologic features, with resulting architecture disruption, doubling of the epithelial monolayer, distorted, uneven cryptic lumen and villous blunting.

It should be stressed that histopathologic features of intestinal acute rejection can be focal or segmental, often localized in the ileum.

Histologic differential diagnosis is often difficult and should be formulated for intestinal graft ischemic injury and CMV enteritis. Ischemic (harvesting, preservation and reperfusion) injury of the intestinal graft usually occurs after 7.5 h of cold ischemia time and consists of focal epithelial denudation of the villi along with congestion or hemorrhage in the lamina propria. These lesions, when reversible, usually heal within 10 days after transplantation.

Chronic intestinal allograft rejection

Histologically, on endoscopic-guided mucosal biopsies, there is a progressive distortion of the mucosal architecture, with villous blunting, widening of the lamina propria, scant cellular infiltrate, severe prominent cryptitis with cryptic cell apoptosis, depletion or loss of goblet and Paneth cells.

In more severe and advanced stages, focal chronic ulcerations, mucosal microabscesses, epithelial metaplasia, fibrosis of the lamina propria, of the submucosa and of the mesenteric lymph nodes (Fig. 10a), along with obliterative arteriopathy of the intestinal arterioles occur, as

demonstrated by full-thickness intestinal biopsies (Fig. 10b).

Graft-versus-host disease

Pathologic monitoring of GVHD is by standard histology, immunohistochemical techniques [immunostaining, sex identification after fluorescence-in-situ hybridization (FISH) and PCR karyotyping ("DNA fingerprinting")]. With these procedures it is possible to differentiate migrating immunocompetent cells of the donor (donor "passenger leukocytes") from recipient cells, as well as to document the immunological injury of the recipient tissue by the donor-infiltrating cells. Inadequate immunosuppression is a major risk factor for GVHD. In spite of the historical fear of a high incidence of GVHD, documented in experimental intestinal transplantation, recent clinical experience has actually shown minor GVHD occurrence (5%).

One of the most intriguing findings from the above analyses is the gradual replacement of the donor hematolymphoid cells in the intestinal wall and mesenteric lymph nodes of the graft by immunocompetent hematolymphoid cells from the recipient (recipient "passenger leukocytes"), which rearrange the normal intestinal mucosal immune system architecture. Conversely, donor migratory immunocytes (donor "passenger leukocytes") from the graft migrate at the same time ubiquitously into the recipient's blood stream and tissues. This new immunological status ("systemic microchimerism") could be the basis of gradual induction of future donor-specific non-reactivity ("tolerance").

Infectious enteritis

Major histologic features of CMV enteritis are giant mucosal epithelial cells with pleomorphic nuclei, harboring basophilic nuclear and cytoplasmic inclusion bodies, mixed inflammatory cell infiltrate, cryptitis, epithelial cell necrosis, apoptosis and villous atrophy (Fig. 6b).

In invasive *Candida* enteritis, subsequent to disruption of the mucosal barrier, histopathological findings show the yeasts or pseudohyphal forms of the fungus within the epithelial layer, the lamina propria or the submucosa (Fig. 7b). Sometimes, in severe and advanced cases, invasive enteric candidiasis is characterized by the presence of microabscesses, with the yeast at the center of the lesion, with a surrounding area of inflammatory cell infiltrate and necrosis.

Imaging findings

Acute intestinal allograft rejection

Radiological criteria are based on gastrointestinal contrast studies, CT scan and gastrointestinal transit and emptying-time evaluations. They consist of enlargement of the intestinal lumen, edema and thickening of the intestinal wall, blunting and loss of the mucosal folds, and paralytic ileus with increased transit and emptying times (Fig. 11).

Chronic intestinal allograft rejection

Radiologically, intestinal contrast studies show a stiff, rigid, tubular appearance of the intestinal loops, sometimes with strictures, flattening or loss of the mucosal folds, paralytic ileus with resultant increased transit and emptying times (Fig. 12a).

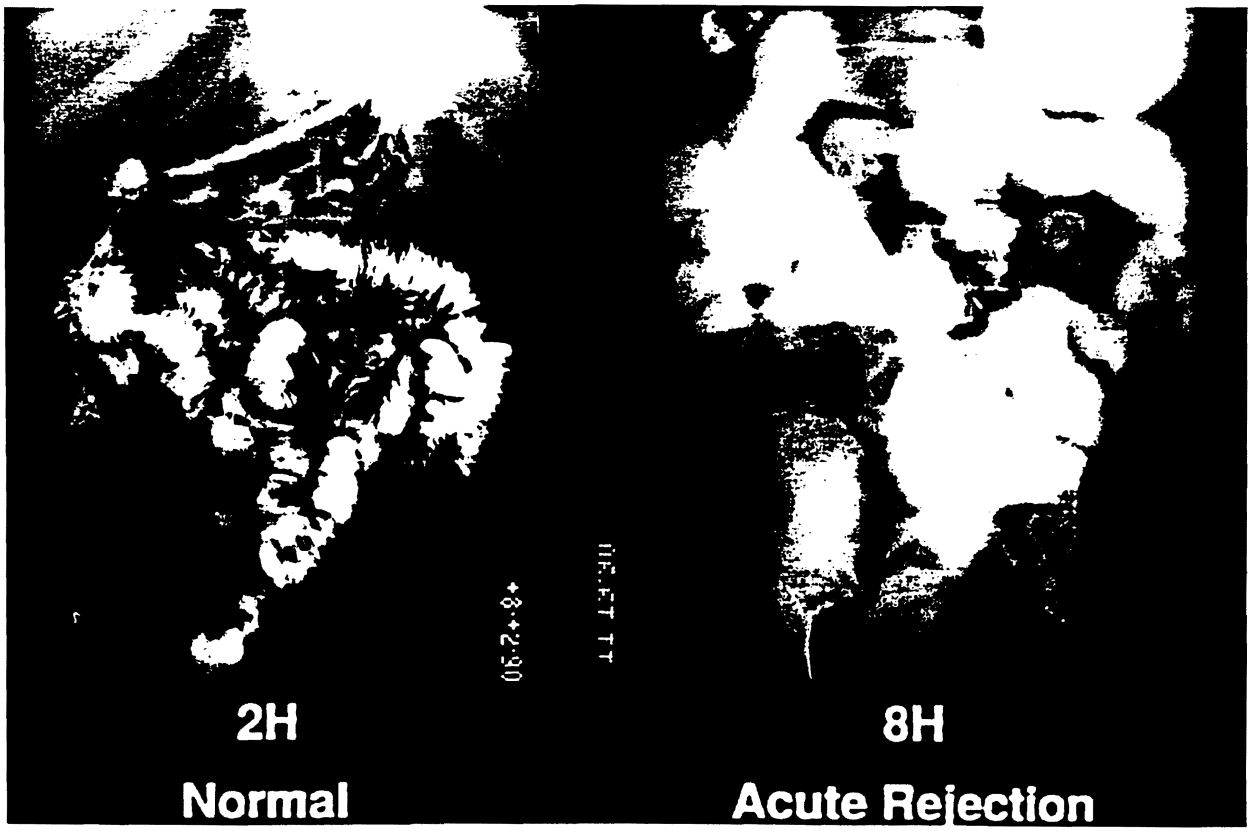
CT scans exhibit the same picture as above, with significant thickening of the intestinal mucosa.

Angiography has revealed segmental stenosis of the mesenteric arterioles (Fig. 12b), validating the obliterative arteriopathy of the delayed long-lasting chronic rejecting intestinal graft (Fig. 10b).

Conclusions

Although human clinical intestinal and multivisceral transplantation has recently become a feasible treatment for patients with chronic, irreversible, end-stage intestinal failure (Table 1), monitoring and management of their early and late post-operative course still remain problematic due to the frequent onset of severe early and late immunological and infectious complications.

Monitoring of the intestinal graft for rejection (mainly ACR) is often difficult and questionable because there are no clearly defined specific clinical and laboratory parameters known to be reliable and of value. Consequently, enteroscopy, endoscopy-guided biopsies,



(a) (b)

Fig. 11 a,b. Radiological patterns of intestinal allograft acute cellular rejection: (a) normal reference appearance; (b) 8 h after the onset of the first clinical symptoms and signs, contrast studies of the transplanted isolated intestinal allograft show dilation of the intestinal lumen, edema and thickening of the intestinal wall, blunting and loss of the mucosal folds, and paralytic ileus with increased transit and emptying times

endoscopic medication and surgery of the graft can play a critical role.

Since the gastrointestinal tract, as well as the lungs, are the only organs which can be visually explored following transplantation, post-transplant monitoring and treatment could be facilitated by looking directly at the gastrointestinal mucosal appearance endoscopically, as well as by obtaining enteroscopically guided mucosal biopsies for histopathology and cultures.

Conversely, enteroscopy of the transplanted intestinal/multivisceral graft still presents some methodological limitations: total endoscopic surveillance of all gastroenteric segments of the entire transplanted graft for diagnostic purposes or for biopsy sampling is not always feasible or safe.

In the intestinal graft, acute cellular rejection lesions are unevenly distributed in a spotty or segmental fashion, often ileal-centered, thus making endoscopy problematic and unsafe to be performed.

Little data exist that define with an appropriate descriptive vocabulary the endoscopic appearance of the intestinal graft and that correlate the properly characterized endoscopic picture of the graft with symptoms and signs of rejection or infection, as well as with the temporal sequence of treatment and clinical evolution of InMvTx recipients. Acceptable reproducibility of the overall endoscopic examination is required to minimize the level of examiner variability and to raise the diagnostic yield of the enteroscopic procedures.

Several frequently encountered endoscopic findings (edema, erythema, erosions, ulcers) are

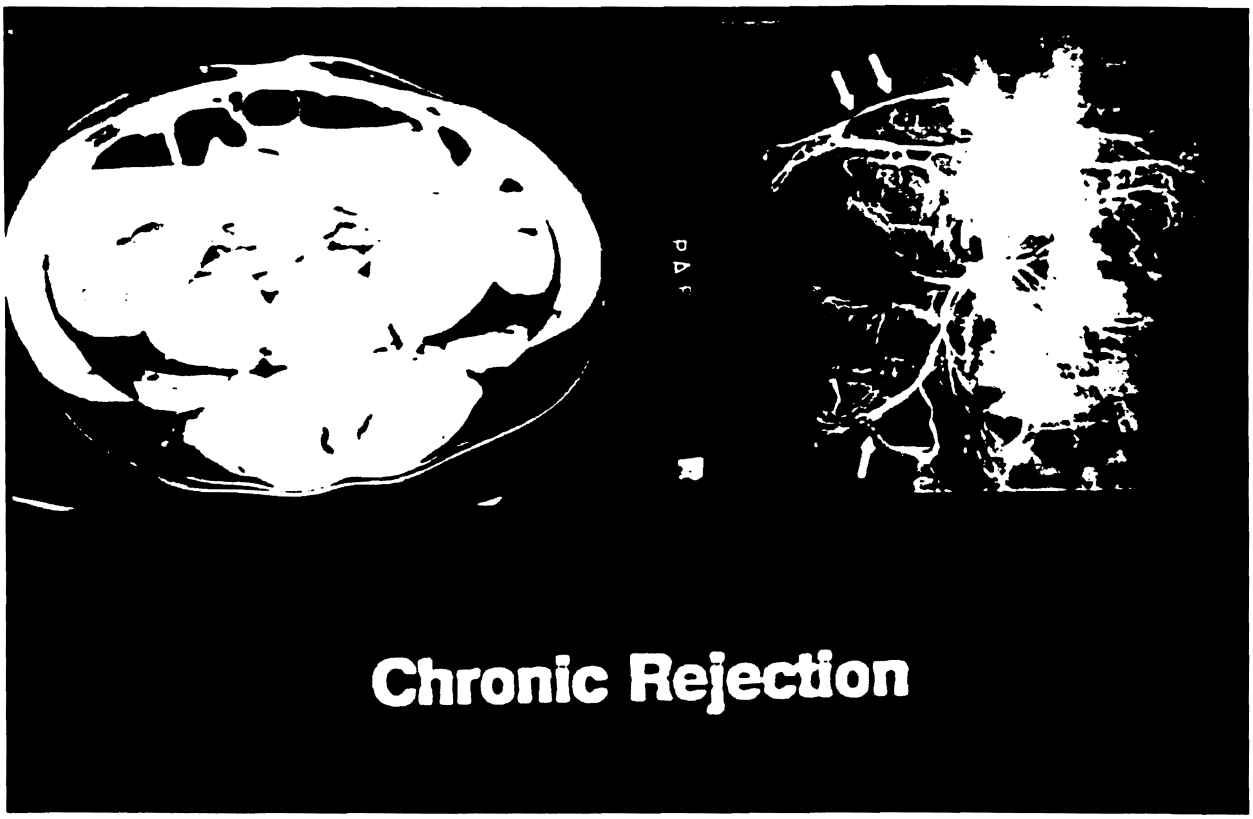


Fig. 12 a,b. "Imaging" features of intestinal allograft chronic rejection: (a) CT scan shows a significant thickening of the intestinal mucosa and of the entire intestinal wall, a stiff, rigid, tubular appearance of the intestinal loops, sometimes with strictures, flattening or loss of the mucosal folds, paralytic ileus with increased transit and emptying times; (b) superior mesentric artery angiography discloses segmental stenosis of the marginal mesenteric arterioles (*arrows*), validating the obliterative arteriopathy of the late chronic rejecting intestinal graft (by courtesy of Lippincot-Raven Publishers, Philadelphia, USA; from: Fung JJ, Abu-Elmagd K and Todo S: Intestinal and Multivisceral Transplantation. In: *Digestive Tract Surgery: a Text and Atlas*, Fig. 35.19, 35.20, p. 1244)

not specific, as both are found in immunological (ACR) and infectious (CMV enteritis) complications.

Finally, the sensitivity, specificity, positive or negative predictive value and diagnostic accuracy of using the endoscopic findings as predictors of the immunological or infectious complications in the intestinal/multivisceral graft have yet to be fully established.

Actually, the endoscopic gross appearance does not always correlate with the endoscopy-guided histopathological findings: Garau et al. have demonstrated that rejection was histologically confirmed in 4 of 91 (4%) procedures with endoscopically normal mucosa, in 6 (9%) of 64 procedures with endoscopic features of inflammation (hyperemia, edema friability, loss of mucosal folds), and in 4 of 29 (14%) of those with endoscopic findings of ulceration.

Hassanein et al. have shown that the only symptom and sign that significantly ($p < 0.05$) correlated with rejection was fever. Similarly, high stomal discharge was very consistent with rejection and very seldom was secondary to CMV infection. On enteroscopic examination, a glistening or velvety appearance of the mucosa, the presence of normal mucosal folds and of normal mucosal vascular patterns were strongly suggestive of a healthy graft. Conversely, mucosal erythema, erosions, ulcers and pseudomembranes were never considered normal: mucosal erythema was a significant

descriptor of rejection, retrieved in 78% of cases of ACR; diffuse ulceration was found in 33% of cases of rejection; focal ulceration with punctuate areas of erythema was a critical sign of CMV enteritis.

Enteroscopy and endoscopy-guided biopsies are valuable in monitoring InMvTx recipients. Because clinical symptoms and signs of rejection and infection are inadequate and inconsistent, monitoring and diagnosis of rejection rely on both clinical judgment and histological findings. Although histopathological criteria still have some limitations due to the patchy distribution of the immunological mucosal lesions and/or the small size of the endoscopy-guided biopsies, they currently represent the gold standard for the diagnosis of the immunological and infectious complications in InMvTx recipients.

In order to improve the diagnostic yield of enteroscopy and to minimize the level of examiner variability, the endoscopic procedures in InMvTx recipients should be performed by very experienced gastroenterologists familiar with endoscopy in patients with intestinal/multivisceral transplantation.

Additionally, the reports of endoscopic procedures done in InMvTx recipients should include easily identifiable features and utilize descriptive terms with a high degree of correlation and reproducibility. Standardized descriptive terminology among endoscopists can minimize the intra- and interexaminer variability, thus increasing the value of enteroscopy as a reliable diagnostic tool in InMvTx recipients.

The sensitivity, specificity, positive or negative predictive value and accuracy of using the most commonly mentioned mucosal endoscopic findings (erythema, edema, erosions, ulcerations, exudates, pseudomembranes, bleeding, friability, granularity) (Table 2C) as predictors of the immunological (ACR) or infectious (CMV enteritis) complications in the intestinal/multivisceral graft have been prospectively studied by Tabasco-Minguillan et al.

The usefulness of a "normal" endoscopy in predicting the absence of significant histopathological findings showed low predictive values. When all the graft regions were considered, a "normal" endoscopy as indicator of the absence of ACR or CMVpresented the following values: sensitivity 55%, specificity 67%, positive predictive value 50%; negative predictive value 71%. Slightly higher values were recorded (sensitivity 56%, specificity 83%, positive predictive value 82%, negative predictive value 59%) when a "normal" endoscopy, as predictor of no ACR or no CMV, was found in the ileal segment of the allograft.

Similarly, the sensitivity, specificity, positive and negative predictive value of ulcers as indicators of ACR, CMV, both or neither have been calculated. When all the grafts were considered, sensitivity (51%) and specificity (71%) in diagnosing ACR were relatively low; the positive predicting value (33%) was also low; the negative predictive value (86%) was higher. When the ileum was considered separately, the sensitivity (100%) and negative predictive value (100%) improved, but specificity (67%) and positive predictive value (33%) did not.

In summary, in a number of cases of intestinal allograft rejection, CMV enteritis or both, the enteroscopic appearance of the intestinal graft has been reported as normal. Consequently, the presence of normal endoscopic features in the intestinal/multivisceral allograft does not exclude immunological or infectious complications.

Considering all graft regions, ulcers present a low sensitivity and a low predictive value for ACR, as they are also found in CMV enteritis. In this setting (all grafts considered), ulcerations are not specific and have a poor positive predictive value in diagnosing rejection. Ulcers in the ileum show improved sensitivity and negative predictive value, decreased specificity and low positive predictive value.

In conclusion, for the time being, enteroscopic examination of the intestinal/multivisceral allograft still presents some methodological limitations: consequently, in InMvTx recipients, endoscopy should not be used as the unique monitoring and diagnostic tool for immunological and/or infectious complications, but it must always be combined with histopathological evaluation, as well as correlated with clinical judgment and "imaging" examinations.

Suggested reading

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