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Is rejection a diffuse or localized process in small-bowel transplantation?

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Abstract. Utilization of endoscopy to both visualize and selectively biopsy an intestinal allograft has become the standard for early recognition and treatment of intestinal allograft rejection. Despite the widespread acceptance of the need for selective mucosal biopsies, it has not been shown that the histological features of intestinal allograft rejection are either localized or occur as part of a more diffuse phenomenon within a tubular allograft.

To resolve these issues, 88 ileoscopies were performed in 12 small-bowel allograft recipients and mucosal biopsy samples were obtained at 5, 10, and 15 cm, respectively, from the ileal stoma. Each mucosal biopsy was labeled, processed, and evaluated individually for the presence and severity of any evidence for allograft rejection.

The data obtained suggest that intestinal allograft rejection is a diffuse process, and biopsies obtained randomly from an ileal graft are likely to demonstrate evidence of allograft rejection when such is present.

Key words: Small-bowel transplantation – Ileoscopy – Biopsy – Acute cellular rejection – Intestinal rejection

Recent advances in surgical technique, together with the introduction and use of FK 506 as the primary immunosuppressive agent, have enabled acceptable success with small-bowel transplantation to be achieved. In most cases, small-bowel transplantation has been applied as therapy for intestinal failure, usually as a result of a short gut syndrome [5, 9, 12]. The early recognition and aggressive treatment of intestinal allograft rejection have been recognized as critical to the ultimate success of such transplants. Endoscopic visualization of the intestinal allograft, together with selective biopsies and histological assessment of the mucosa of the graft, has been reported to be very effective at identifying intestinal acute cellular rejection (ACR). They are also useful for identifying other pathologies such as CMV enteritis and chronic rejection, each of which requires a different therapeutic response [1, 2, 6–8].

Of particular interest in the clinical situation is the fact that in at least 90% of the cases, the endoscopic appearance of the allograft enables immediate therapy of ACR to be initiated before the diagnosis can be confirmed histologically [13]. However, currently, it is not known whether histologic allograft rejection, when present, is either a localized or a diffuse phenomenon.

In order to address the issue of diffuse vs. local acute cellular rejection, the following study was performed.

Materials and methods

Patient material. The patient population studied consisted of seven females and five males having a mean age of 37.5 years (range 19–50 years). Five patients were isolated small-bowel transplant recipients; five had received a small-bowel graft in conjunction with an orthotopic liver transplant; the final two had a multivisceral organ transplant which included the small bowel, liver, pancreas, stomach, and duodenum.

Between July 1, 1992, and December 31, 1992, 88 ileoscopies were performed on 12 adult small-bowel allograft recipients for clinical indications. During each ileoscopy, the ileal graft was biopsied at 5, 10, and 15 cm, respectively, from the ileal stoma, in order to identify the presence and intensity of any histologic evidence for acute cellular rejection. A total of 264 mucosal biopsy samples were examined. Each biopsy was fixed in 10% formalin, dehydrated, sectioned at 5 μm, and stained with hematoxylin and eosin. Each was

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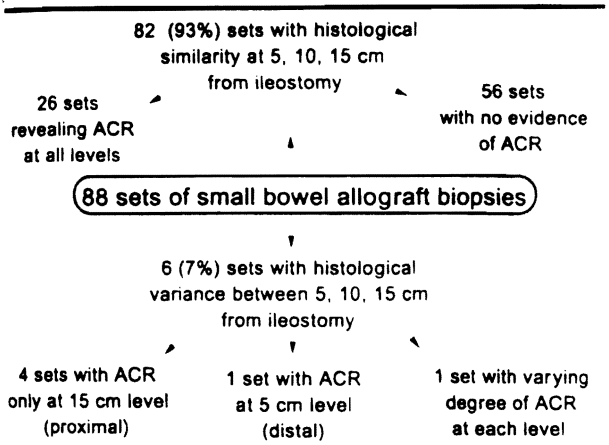

Fig. 1. Schematic showing the results of 88 sets of small-bowel allograft endoscopic biopsies.

examined by an experienced staff pathologist at the University of Pittsburgh Medical Center.

In four patients, biopsies of the allograft jejunum were obtained as well as the three ileal biopsies obtained routinely.

Patient preparation. The patients were given nothing by mouth for 8 h prior to each ileoscopy. On rare occasions, a few patients required a saline enema prior to the ileoscopy to evacuate the stool present in the graft, enabling adequate visualization of the mucosa. All procedures were performed in the morning before 9:00 AM so that the histologic findings would be available by late afternoon of the same day.

Histologic criteria for intestinal allograft rejection. The criteria utilized for identifying intestinal allograft rejection were those developed in animal models [4]. These are as follows: Mild to moderate acute cellular rejection is characterized by a mononuclear cell infiltrate of the mucosa associated with villus blunting, epithelial cell damage, and regeneration and a reduction in the amount of epithelial cell mucus and Paneth cells in the mucosa. Severe acute cellular rejection is characterized by mucosal hemorrhage, overt mucosal sloughing, and crypt distruction [3, 10, 11].

Results

The results of this study are shown schematically in Fig. 1. In 82 of 88 (93%) sets of ileal graft biopsies, the histopathological findings were similar at all three biopsy sites. Of these, 26 were remarkably consistent with the histologic rejection varying in degree only from mild to moderate. Six sets of biopsies showed some degree of internal variability between the three biopsy sites. Of these six sets, four sets revealed minimal to mild rejection at the most proximal location (15 cm) while no evidence for acute cellular rejection was detected at the more distal 5- and 10-cm locations. In one set, the histologic severity of the acute rejection was more prominent at the most distal (5 cm) site. In the remaining set, the histologic evidence for acute cellular rejection was most prominent at the 5-cm level while the 10- and 15-cm sites demonstrated a milder degree of rejection.

Four of these 88 ileoscopies were performed in combination with an upper gastrointestinal endoscopy

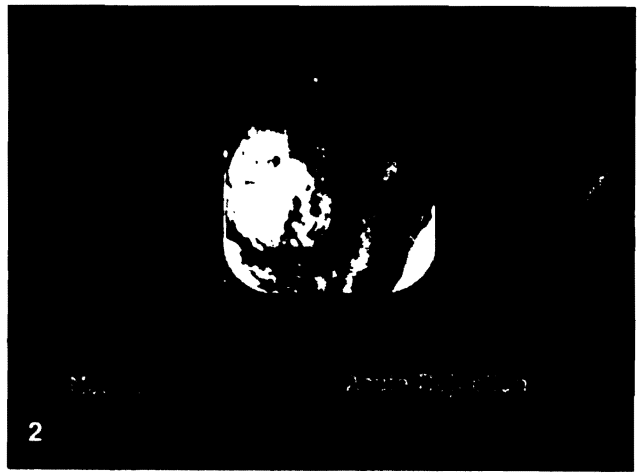

Fig. 2. Photographs of the endoscopic appearance of intestinal allografts showing a normal allograft appearance on the left, mild acute cellular rejection in the middle, and severe acute cellular rejection to the right.

Fig. 3. Photograph of the endoscopic appearance of an intestinal allograft with C-difficile enteropathy to the left and mild and severe chronic allograft rejection in the middle and right, respectively.

with biopsies being obtained from the allograft jejunum. In all four cases, the biopsies obtained from the allograft jejunum demonstrated a histopathology similar to that of the ileal graft. In two, acute cellular rejection was identified in all three biopsies obtained from the distal ileal allograft as well as the very proximal jejunal portion of the intestinal allograft. In the other two cases, neither the jejunal nor ileal sites had any histologic evidence for rejection.

The presence of histologically confirmed rejection was associated with clinical findings of a sudden change in patient mood, the presence of fever and abdominal pain, the onset of a stomal discharge, and the presence of diarrhea with or without blood. Endoscopically, the areas of intestinal allograft rejection could be identified as being ischemic (pale) or dusky because of the presence of edema, mucosal sloughing, bleeding, and a local area of reduced or absent peristalsis.

The endoscopic appearance of intestinal allograft rejection as compared to normal bowel and acute and chronic allograft rejection and C-difficle allograft enteropathy is shown in Figs. 2 and 3. The normal al-

lograft has an entirely normal appearance. In contrast, in acute rejection, the bowel first becomes granular and thickened as a result of edema and then overtly hemorrhagic (Fig. 2). In chronic rejection (Fig. 3) the allograft bowel demonstrates a similar granular appearance as seen in early ACR, but also demonstrates a loss of the valvulae and reduced or absent peristalsis. With late chronic rejection, enhanced granularity and mucosal ulcers are seen. As occurs in the colon, C-difficle enteropathy is associated with the presence of flat white pseudomembranes that adhere to the mucosal surface (Fig. 3).

Discussion

Since small-bowel transplantation has been introduced clinically, its success has been shown to parallel the ability of the treating physicians and nurses to identify and treat rejection. Endoscopic biopsies have been shown to be extremely valuable for this purpose. Usually ileal biopsies have been used for this purpose because of the ease with which they can be obtained. Whether a biopsy obtained from the terminal ileum represents the status of the whole allograft remains a concern. This important issue has been addressed in the present study, in which allograft mucosal biopsies were obtained at 5, 10, and 15 cm, respectively, from the stoma of the terminal ileum as well as from the jejunal portion of the graft in four cases.

The data obtained suggest that intestinal allograft rejection when it occurs is a diffuse process and biopsies obtained randomly from any site in the ileum are likely to represent the rest of the graft at least when it comes to documenting the presence or absence of allograft rejection. In unusual cases, the histologic findings of acute cellular rejection can be limited in location but are unlikely to be missed if multiple blind or endoscopically directed biopsies are obtained and assessed histologically.

Based upon these findings, it can be stated that random mucosal biopsies from the distal segment of an intestinal allograft can be obtained easily and should be the routine in patients suspected of having an episode of intestinal allograft rejection.

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