ditioning regimen by modulating mixed chimerism induction and immune reconstitution. Transplantation 2003;75:2135-43.
9. Morishima Y, Kodera Y, Hirabayashi N, Tanimoto M, Matsuyama T, Horibe K, et al. Low incidence of acute GVHD in patients transplanted with marrow from HLA-A,B,DR-compatible unrelated donors among Japanese. Bone Marrow Transplant 1995;15:235-9.

Stem Cell Transplantation

New insights into the pathophysiology of gastrointestinal graft-versus-host disease using capsule endoscopy

We investigated gastrointestinal graft-versus-host-disease using capsule endoscopy in patients with abdominal pain and/or diarrhea. We found severe pathology involving most of the gut including loss of villi, ulcerations, narrowing, bleeding and fistula formation. In 2 patients, capsule endoscopy alone established the diagnosis of graft-versus-host-disease. Some ulcerations were associated with cytomegalovirus infection.

haematologica 2005; 90:1003-1004
(*http://www.haematologica.org/journal/2005/7/1003.html*)

Fourteen patients with gastrointestinal graft-versus-host disease (GVHD)) acute (n=11), or signs of chronic GVHD with diarrhea, abdominal pain or malabsorption (n=3) were studied by using capsule endoscopy. GVHD was graded according to the International Bone Marrow Transplant Registry (IBMTR) indices.[1] Routine stool examinations were done. The median grade of acute gastrointestinal-GVHD was C (range B-D). Two of the patients had reactivation of cytomegalovirus (CMV) diagnosed by pp65 antigenemia, while one had borderline results. Capsule endoscopy is the only minimally invasive method for direct visualization of the entire small intestine. The system uses a disposable miniature video camera contained in a capsule, which is ingested by the patient. The capsule passes through the digestive tract, transmitting high quality color images during 6-7 hours. Capsule endoscopy has been proven to be effective in the diagnosis of diseases of the small bowel such as tumors and inflammatory bowel disease and in identifying the source of gastrointestinal bleeding.[2,3] In this study we used a GIVEN M2A capsule (Yoqneam, Israel) which was ingested after a 12-hour fast and 30 minutes after administration of metoclopramide. Patients were followed for abdominal symptoms with attention to the stool to identify the capsule. No symptoms of obstruction were recorded and all the capsules were retrieved. One patient died 7 days after capsule endoscopy due to sepsis. There

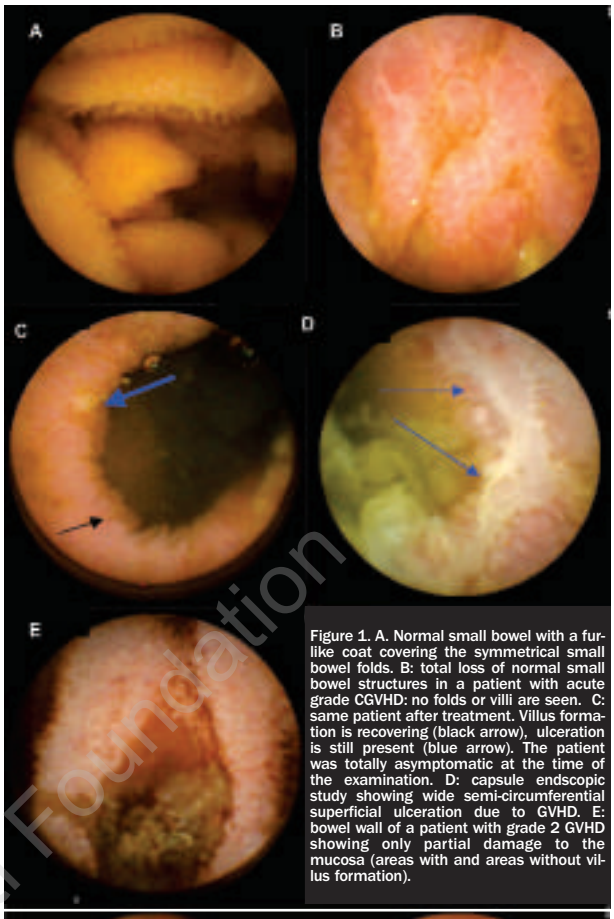

Figure 1. A. Normal small bowel with a fur-like coat covering the symmetrical small bowel folds. B: total loss of normal small bowel structures in a patient with acute grade CGVHD: no folds or villi are seen. C: same patient after treatment. Villus formation is recovering (black arrow), ulceration is still present (blue arrow). The patient was totally asymptomatic at the time of the examination. D: capsule endscopic study showing wide semi-circumferential superficial ulceration due to GVHD. E: bowel wall of a patient with grade 2 GVHD showing only partial damage to the mucosa (areas with and areas without villus formation).

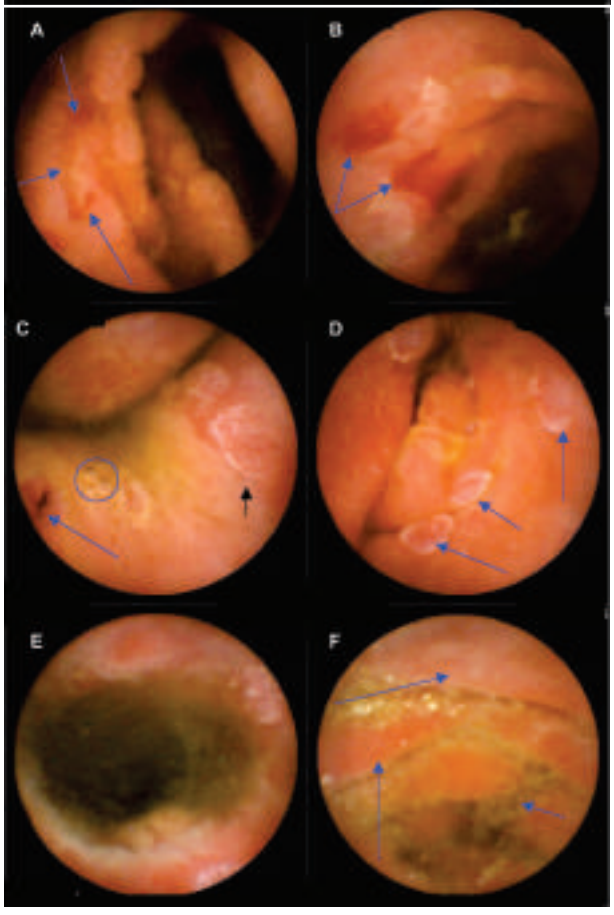

Figure 2 [right column, low panel]. A: small bowel with deep ulceration between the blue arrows, most probably due to CMV infection; this patient had positive pp65 CMV antigenemia. B: small bowel wall lacking villi with spontaneous bleeding (blue arrows). C: intestinal mucosal covered with multiple diffuse aphthous lesions (blue arrows) in a patient with grade 4 GVHD; no villi can be seen. D: same patient as in picture 2C with aphthous lesions (short black arrow). The orifice of an entero-enteric fistula can be seen (long blue arrow); note the air bubbles (circled), which exit via the fistula. E: circumferential luminal narrowing in a patient with grade 4 GVHD; note the absence of villi and peripheral aphthous lesions. F: irregular thickened folds, with mucoid discharge adherent to surface of the mucosa in a patient with grade 4 GVHD. Typically, villi are absent.

was no endoscopy-related morbidity.

Patients with acute GVHD had severe damage to the small bowel mucosa and the extent of the damage correlated with the grade of GVHD. Patients with grade D GVHD had disease involving the entire small bowel. Mucosal findings included loss of villi and small bowel folds, superficial mucosal breaks, spontaneous bleeding, ulceration, stricture formation and lack of peristalsis (Figures 1 and 2). Five patients had lack of stomach peristalsis without overt lesions. Patients with CMV antigenemia had typical deep ulcerations with sharply demarcated borders; the same findings were present in the patient with borderline antigenemia, in whom bowel biopsy subsequently proved the CMV bowel infection. In one patient with grade D GVHD an entero-enteric fistula was diagnosed (Figure 2C). In 2 patients, acute GVHD was clinically suspected without biopsy support, however, the capsule endoscopy made the diagnosis possible by showing the typical features of acute GVHD demonstrated in this study. One patient with severe acute GVHD responding to treatment underwent a repeat capsule endoscopy demonstrating regenerated villi, although the entire bowel was severely diseased with scattered ulcerations (Figures 1B and 1C). Lesions were less severe and extensive in the cases with grade B-C GVHD. No significant mucosal abnormalities were identified in chronic GVHD.

Gastric transit time (TT) was increased in patients with acute GVHD, being an average of 119 minutes (range 2–310). In 3 patients with stage D acute GVHD, gastric TT was extremely prolonged. The average gastric TT in healthy volunteers was 32 minutes (range 1-164) (p=0.016). Average small bowel TT was 268.4 minutes (range 122–375) and was normal in patients with chronic GVHD (average 240, range 201-304 minutes). In spite of the now considerable understanding of the cellular and cytokine pathogenesis of GVHD, knowledge regarding the physiology and macroscopic histopathology of active *in vivo* gastrointestinal GVHD is lacking.[4] In this study, we have found that acute GVHD (especially grade D) of the stomach led to gastroparesis which, surprisingly, was not always clinically evident. Small bowel peristalsis was also severely affected and bowel TT was prolonged even in the presence of profuse diarrhea. This may indicate that the inflammation in the gut wall interferes with enteric nerve signaling resulting in a *stunned intestine*. Capsule endoscopy showed characteristic mucosal damage including diffuse superficial mucosal disease, loss or shaven villi, mucosal breaks, vascular malformation, mucosal hemorrhages, ulcerations, inflammatory exudates, bleeding, scalloped folds and aphthous lesions (Figures 1 and 2) although a tissue biopsy could not be obtained the from the precise spot where the diagnostic endoscopic picture was seen. Capsule endoscopy revealed new findings previously not described in patients with acute GVHD including strictures and an entero-enteric fistula indicating that the inflammatory process infiltrates the entire small bowel wall. No significant mucosal abnormalities were identified in chronic GVHD. The only visible phenomena were mild focal loss of villi and thickened villi. Viewing the endoscopic pictures, it seems that grade C-D GVHD is a separate entity in which the mucosal villi are entirely destroyed (Figure 1B). Villous regeneration occurs in response to medical therapy of GVHD, and this is accompanied by a resolution of diarrhea, although the integrity of the small bowel mucosa remains compromised thus providing a port of entry for pathogens. Interestingly, we identified deep ulcerations indicative of CMV infection only in those patients in with CMV antigenemia. This may imply that the capsule endoscopy is an important tool in the identification of intestinal CMV infection and may help to differentiate GVHD from CMV, a significant clinical issue considering the fact that the treatment is different (increasing vs. decreasing immunosuppression).

We conclude that capsule endoscopy in GVHD is feasible and safe; it may be a simple non-invasive method to diagnose acute GVHD and define the extent of bowel involvement neither of which can be achieved by colonoscopy. Although colonoscopy is cheaper then capsule endoscopy and facilitates biopsy, it may provide less information and carries a higher risk of bleeding if biopsy is done. The routine use of capsule endoscopy may provide early diagnosis and better care for allogeneic stem cell transplant recipients with gastrointestinal symptoms, and thus improve transplantation results. Considering the poor gastric motility in these patients, we recommend the use of prokinetics before the capsule endoscopy and also suggest placing the patient in the right lateral position for at least 30 min after swallowing the capsule in order to facilitate its gastric passage.

Michael Y. Shapira, Samuel N. Adler,° Harold Jacob,° Igor B. Resnick,* Shimon Slavin,* Reuven Or**

**Department of Bone Marrow Transplantation & Cancer Immunotherapy, Hadassah, Hebrew University Medical Center; °Department of Gastroenterology, Bikur Cholim Hospital, Jerusalem, Israel*

Key words: allogeneic stem cell transplantation, graft-versus-host disease, capsule endoscopy, gastroparesis, bowel motility, stunned intestine.

Correspondence: Michael Y. Shapira MD, Department of Bone Marrow Transplantation, Hadassah, Hebrew University Medical Center, PO Box 12000, Jerusalem, Israel, 91120. Phone: international +972.2.6778351. Fax: international + 972.2.6777540. E-mail: shapiram@hadassah.org.il

References

1. Martino R, Romero P, Subira M, Bellido M, Altes A, Sureda A, et al. Comparison of the classic Glucksberg criteria and the IBMTR Severity Index for grading acute graft-versus-host disease following HLA-identical sibling stem cell transplantation. International Bone Marrow Transplant Registry. Bone Marrow Transplant 1999;24:283-7.
2. Eliakim R, Adler SN. Capsule video endoscopy in Crohn's disease - the European experience. Gastrointest Endosc Clin N Am 2004; 14:129-37.
3. Lewis B, Goldfarb N. The advent of capsule endoscopy: a not-so-futuristic approach to obscure gastrointestinal bleeding. Aliment Pharmacol Ther 2003;17:1085-96.
4. Reddy P. Pathophysiology of acute graft-versus-host disease. Hematol Oncol 2003;21:149-61.
5. Sullivan KM, Graft-versus-host-disease. In: Blume KG, Forman SJ and Appelbaum FR, editors. Thomas' hematopoietic cell transplantation, Blackwell Scientific Publication, 2004, (Cambridge, Massachusetts, USA). p. 639.
6. Evans J, Percy J, Eckstein R, Ma D, Schnitzler M. Surgery for intestinal graft-versus-host disease: report of two cases. Dis Colon Rectum 1998;41:1573-6.