Usefulness of magnifying endoscopic evaluation of the terminal ileum for a patient with graft-versus-host disease after allogeneic hematopoietic stem cell transplantation

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Abstract

The gastrointestinal tract is one of the common targets of acute GVHD, but accurate diagnosis is difficult because of the nonspecific nature of complicated diseases and the lack of diagnostic findings by conventional endoscopy. Recently, a magnifying endoscope has been developed and used for examining microstructures of the mucosa. Herein, we report the first use of a magnifying endoscope for a patient with GI GVHD. Magnifying endoscopic findings of atrophic and coalescent villi of the terminal ileum reflect histological findings of GVHD. Magnifying endoscopy of the terminal ileum may be useful for early detection and following-up of GI GVHD.

Key words: hematopoietic stem cell transplantation, gastrointestinal GVHD, magnifying endoscopy, terminal ileum

Introduction

Graft-versus-host disease of the gastrointestinal tract (GI GVHD) is a major cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation. Previous studies suggested that endoscopic evaluation, with histological examination of biopsied tissue, is required for accurate diagnosis of GI GVHD. However, it is still not clear whether conventional histological diagnosis of GI GVHD can be predicted from conventional endoscopic findings. Conventional endoscopic findings have been reported to be normal in up to 21 % of patients with histologically confirmed GI GVHD [7, 10].

Recently, a magnifying endoscope, the zooming capability of which is the same as that of a stereomicroscope (x 80-100), has been applied to observation of mucosal microarchitecture in patients with various intestinal diseases, such as inflammatory bowel disease and early colorectal cancer [5]. The use of magnifying endoscopy for surveillance of rejection in a patient who had undergone allogeneic small intestine transplantation has also been reported [9]. Herein, we report the first use of a magnifying endoscope for surveying GI GVHD. Magnifying endoscopy of the terminal ileum may be useful for early detection and following-up of GI GVHD.

Case report

An 18-year-old male patient with acute lymphoblastic leukemia received an allogeneic bone marrow transplant from an HLA-matched unrelated donor in his first complete remission in August 2001. The conditioning regimen consisted of cyclophosphamide, etoposide, and total body irradiation (Cy+VP+TBI). Short-term methotrexate and cyclosporin A were administered for GVHD prophylaxis. Hematological engraftment was

observed on day 16 after BMT. He suffered from diarrhea, abdominal pain, skin rash and fever on day 19. GVHD was strongly suspected from his clinical course. Conventional endoscopic study of the upper GI could not detect any abnormality. Due to thrombocytepenia on the day of the study, the biopsy did not carry out. Lower GI study by the use of a magnifying endoscope (EC450ZH x100: Fujinon Toshiba ES Systems Co., Ltd. Tokyo, Japan) on day 31 showed no abnormalities in the colon and villi of his terminal ileum under a conventional view (Fig. 1A). On the other hand, a magnified view revealed abnormalities in villi (coalescence and atrophy). Villi were irregular in both size and shape (Fig. 1B). Endoscopic mucosal biopsy revealed apoptotic bodies of villi and T lymphocyte infiltration to the lamina propria, corresponding to grade 2 GI GVHD according to Sale's pathological classification [8] (Fig. 1C, D). Immunohistochemical staining for CMV was negative. Therefore, we diagnosed the patient as having GI GVHD and prescribed predonisolone at 1 mg/kg. According to Glucksberg's scoring system, clinical symptoms of GVHD were grade 2 (diarrhea: stage 1, skin: stage 1, liver: stage 0) [3]. Following treatment with predonisolone, the patient's clinical symptoms improved and his fever subsided. Improvement in villi of the terminal ileum was observed by magnifying endoscopy on day 71 (Fig. 2A). This was also confirmed by histologic findings (Fig. 2B). There has been no recurrence of GI GVHD and the patient has been well for two years without relapse or chronic GVHD.

Discussion

Criteria for diagnosis of GI GVHD based on conventional endoscopic findings are quite non-specific, such as erythema, edema, erosion, bleeding [1, 2]. Sloughing of the mucosa is a highly specific but infrequent finding that reflects a most severe form of GI

GVHD [6]. There are discrepancies between these nonspecific mucosal findings by conventional endoscopy and histological findings. A few studies have addressed the spectrum and prevalence of these endoscopic features in patients with histologically confirmed GVHD [1, 2, 6, 7, 10]. Some studies have shown a weak correlation between conventional endoscopic findings and histological diagnosis of GVHD [1, 7, 10]. Since there are only a few diagnostic findings by conventional endoscopy, mucosal biopsy by guesswork is currently recommended even if the appearance of the mucosa is normal [4]. Although endoscopy with biopsy is commonly used for the evaluation of suspected GI GVHD, endoscopic biopsy does not always enable early diagnosis of GVHD because GVHD occasionally starts in a segmental fashion, i.e., skip lesion. It is important to note that discordance may be seen in the severity of disease between organs as well as in different regions of the gut. Even if a specimen is obtained from a “hot spot” of GVHD, a small biopsy specimen might not contain a sufficient amount of mucosa to diagnose GVHD. Endoscopic biopsy also involves a risk of bleeding because of the frequent occurrence of thrombocytopenia in patients after BMT [6]. Optimal number, size and sites of biopsy remain controversial. Stomach or rectal biopsy has been reported to be of high diagnostic value for GI GVHD [6, 7]. On the other hand, Terdiman et al. reported high diagnostic value of terminal ileum biopsy, showing a high sensitivity of 90-100% [10]. The terminal ileum is composed of lymphoid tissues and is thought to be a sensitive site showing early signs of GI GVHD.

We used magnifying colonoscope type EC450ZH (Fujinon Toshiba ES Systems Co., Ltd. Tokyo, Japan). The out side diameter of the tip is 13.0mm same as conventional colonoscopy. A soft plastic hood of depth 2mm was attached to the distal end of the endoscope to maintain the correct distance from the target tissue and to enable the

maximal x100 observation. The scope was moved to the cecum by conventional procedure. When the scope introduced through Bawhin valve, distilled water was applied onto the lesion to wash out the overlying mucus and residues via the working channel of the scope. Then a 0.2% indigocarmine solution was sprayed, as a coloring agent for the contrast method. Magnification of the object is possible by one-touch with a lever at hand.

Magnifying endoscopy has been applied to observation of mucosal microarchitecture in patients with various intestinal diseases, such as inflammatory bowel disease and early colorectal cancer [5]. The use of magnifying endoscopy for surveillance of rejection in a patient who had undergone allogeneic small intestine transplantation has also been reported [9]. However, there have been no studies on the usefulness of magnifying endoscopy for evaluating GI GVHD. The histological similarity between GI GVHD and acute small bowel allograft rejection suggests magnifying endoscopy may have a role in diagnosis and following-up for GI GVHD.

Magnifying endoscopy is useful in that it more accurately reflects histological findings than does conventional endoscopy. Subtle mucosal changes that could not be detected by conventional endoscopy were visible by magnifying endoscopy. Magnifying endoscopy can reveal 3-dimensional microstructures of the ileum villi, while conventional endoscopy can reveal only the existence of villi. Magnifying endoscopy may enable *in-situ* evaluation of mucosal morphology and assist in selection of an appropriate site of biopsy. Histologic changes of GI GVHD include apoptosis of epithelial cells (apoptotic body), dropout and uitimately disappearance of villi, and patchy lymphocytic infiltration to crypt (cryptitis) or lamina propria. Atrophic and coalescent changes of villi reflect histological findings of epithelial apoptosis, which is thought to be an early change of GI

GVHD. Widened and erythematous findings of the crypt area reflect cryptitis and mononuclear infiltration in the lamina propria. In our case, upper GI and colorectal survey by conventional endoscopy showed no abnormalities and morphological evaluation by magnifying endoscopy of the terminal ileum with biopsy was quite valuable.

Our case suggests that magnifying endoscopy of the terminal ileum may be useful for detecting GVHD in the early stage. Magnifying endoscopy enables detection of subtle changes in villi and accurate diagnosis of GI GVHD and can therefore minimize the requirement of biopsies and related risk of bleeding. The true value of this technique can only be established by a larger series comparing the pathology of biopsies of mucosa, which are normal versus abnormal by magnifying endoscope in the same patient.

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Figure legends

Fig. 1A. Conventional view at time of diagnosis of GI GVHD.

There are no findings suggesting the existence of GI GVHD.

Fig. 1B. Magnifying view at time of diagnosis of GI GVHD.

Magnifying endoscopy revealed morphological abnormality of villi. Coalescent and atrophic changes of villi and widened crypt areas were observed. Indigo carmine was scattered to enhance the contrast.

Fig. 1C. Pathological findings at time of diagnosis of GI GVHD (HE ×200).

Shortning of villi and dense lymphocyte infiltration into the lamina propria were observed.

Fig. 1D. Pathological findings (HE ×400).

Apoptotic body of villi is shown (arrow).

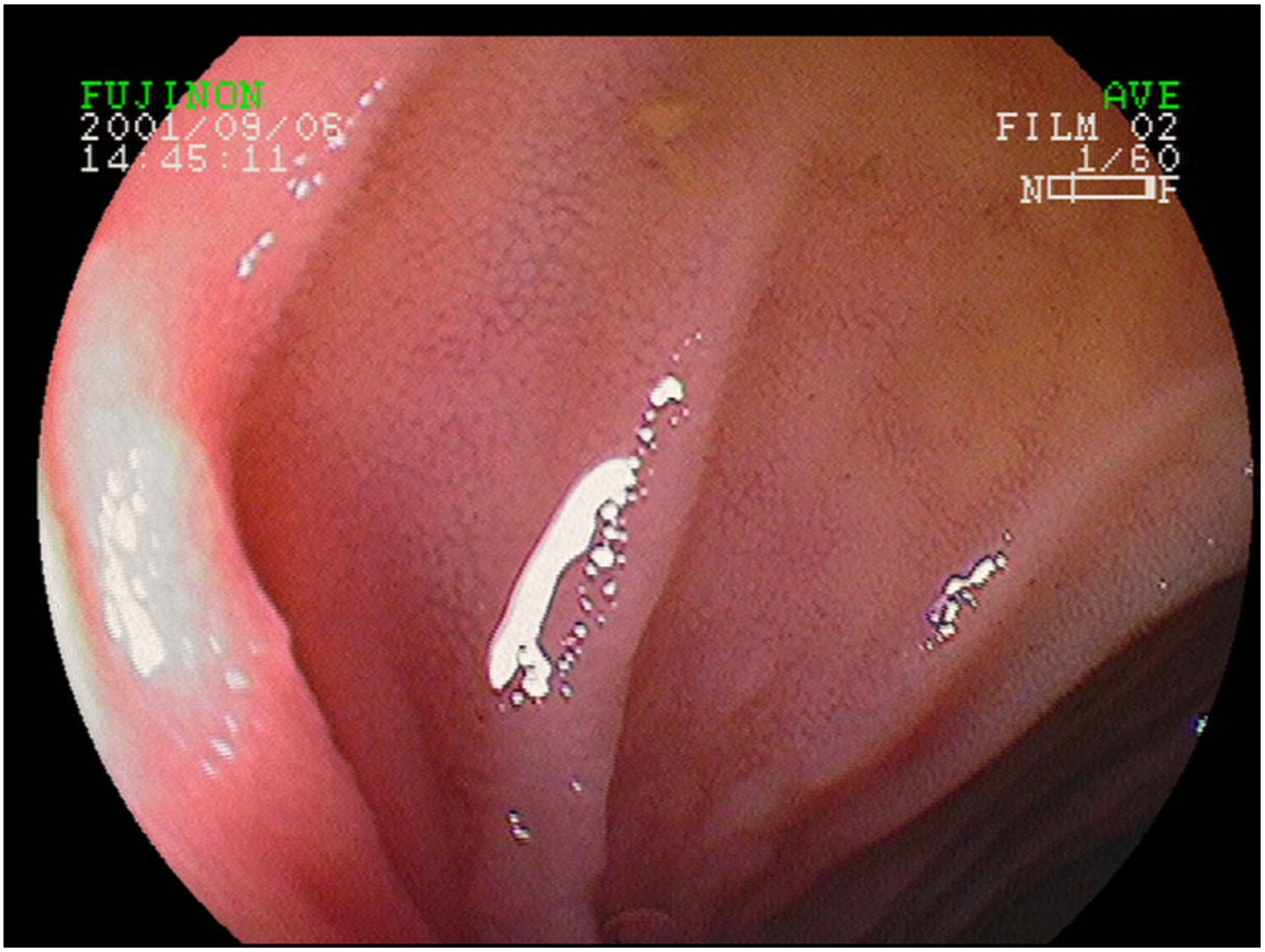
Fig. 2A. Magnifying view of villi after treatment.

Homogeneous and elongated villi with a tight crypt area are shown.

Fig. 2B. Pathological findings after treatment (HE ×200).

There are no findings of GVHD. (The superficial mucosa was torn from the lamina

proplia by artificially at the time of a biopsy. The improvement of the finding of the lamina proplia was also checked by another biopsy sample.)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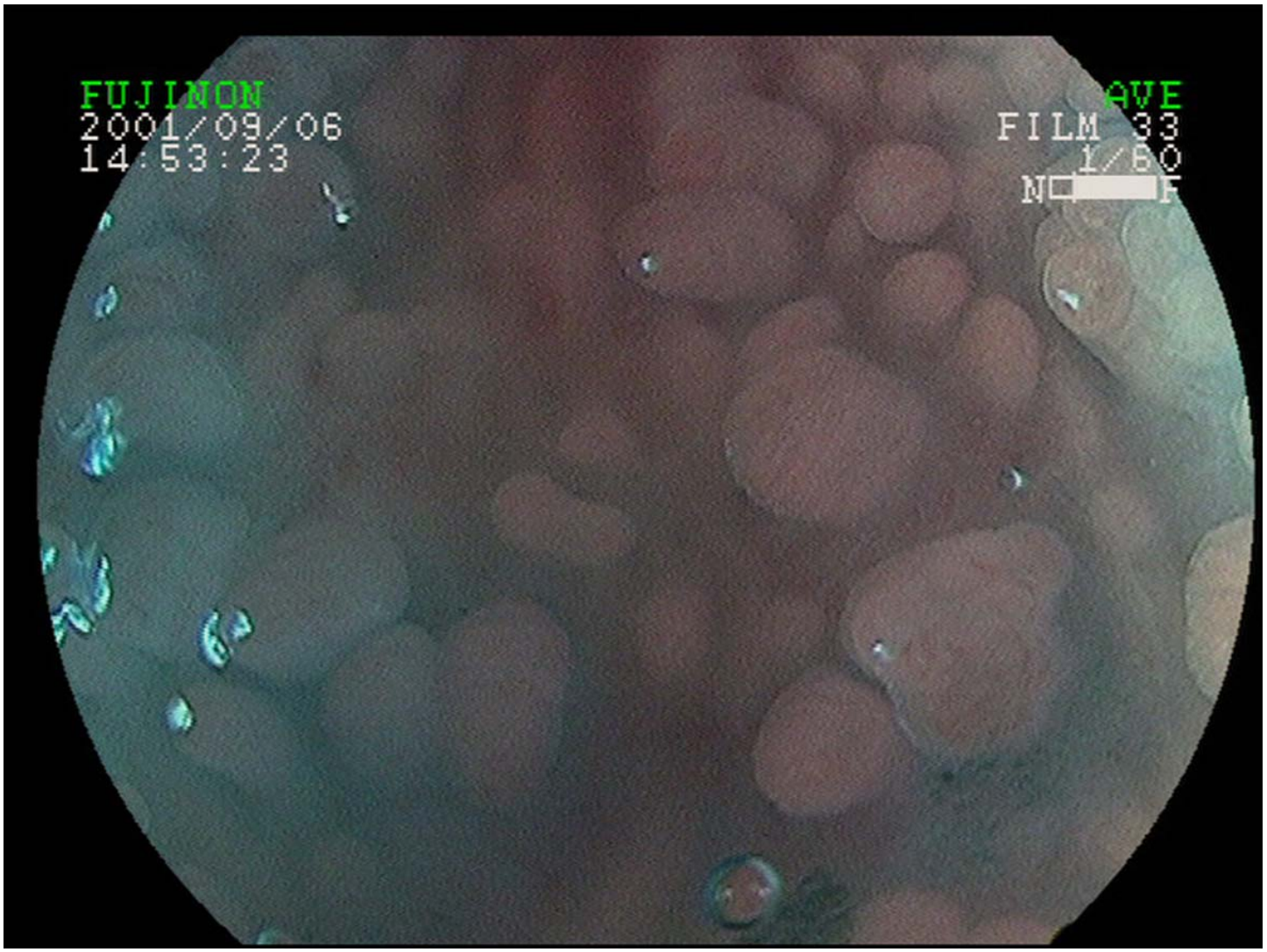
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