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Original contribution

Acute graft-versus-host disease is more prevalent and severe in the lower than the upper gastrointestinal tract☆

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Summary It is unclear whether acute gastrointestinal (GI) graft-versus-host disease (GVHD) affects all segments of the GI tract equally. Up to 45% patients reported showed discrepancy in involvement between upper GI (UGI) and lower GI (LGI) tract. We compared the prevalence and the severity of acute GVHD in UGI and LGI tract on histologic examination. A cohort of 110 cases of simultaneous UGI and LGI biopsies from 105 allogeneic hematopoietic stem cell transplantation recipients with clinically confirmed GI GVHD were reviewed retrospectively. The χ^2 test and 1-way analysis of variance test were used for statistical analysis. Most (75%) of the cases had GVHD involvement in both UGI and LGI tracts, whereas UGI-only GVHD was found in 6% and LGI-only GVHD in 19%. GVHD prevalence was the lowest in stomach (61%) and significantly increased toward duodenum/jejunum (81%; $P = .0019$). The LGI tract showed similar GVHD prevalence ($P = .3648$); the highest was in the sigmoid colon (97%). The histologic grade was lowest in the stomach (mean ± SD, 1.6 ± 0.8) and was similar across all UGI segments ($P = .0883$). The histologic grade in LGI significantly increased ($P = .0265$) from the terminal ileum (2.0 ± 1.3) to the rectum (2.9 ± 1.0). Overall, both the prevalence and the histologic grade of GVHD in LGI were significantly higher than those of UGI ($P < .0001$ for both). Our results show that acute GVHD had a higher prevalence and was more severe in the LGI than in UGI tract. A small subset of patients had only UGI involvement.

1. Introduction

Acute graft-versus-host disease (GVHD) after allogenic hematopoietic stem cell transplantation (HSCT) is a systemic disease that often involves the gastrointestinal (GI) tract. Clinical presentation and endoscopic findings of acute GI GVHD are nonspecific and overlap significantly with other GI diseases that are also common in HSCT recipients [1–6]. Thus, the diagnosis of acute GI GVHD relies on the histologic evaluation of GI biopsies. The histopathologic hallmark of acute GI GVHD is epithelial cell apoptosis [1,7–10].

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Differences in acute GI GVHD diagnosis occur when histopathologic features of GVHD are only seen in biopsies from selected anatomic area(s) of the GI tract. Such a differences between biopsies of the upper GI (UGI) tract and the lower GI (LGI) tract have been reported in up to 45% of patients [3,11]. When disagreement occurred, several studies suggested that the rectum or rectosigmoid colon was more likely to show changes of GVHD than the UGI tract [1,5,8,11–13]. However, other studies advocated that the stomach was the most common site of involvement [3,4,10,14]. These conflicting results suggest that although acute GVHD may affect the entire GI tract, there may be regional difference in susceptibility to GVHD injury. They also demonstrate that a consensus as to which segment(s) of the GI tract is more likely to show histopathologic features of GVHD has not been established.

In this study, we retrospectively surveyed the prevalence of GVHD diagnosis and the histologic grade of acute GI GVHD lesion in various anatomic areas of the GI tract by evaluating 110 cases of simultaneous UGI and LGI biopsies from HSCT recipients with clinically proven acute GI GVHD. The goal of this study is to systemically examine and compare the frequency and the severity of injury in upper and lower segments of the GI tract in a large cohort of acute GI GVHD patients.

2. Materials and methods

Study approvals were obtained from the institutional review boards at the University of Pittsburgh, School of Medicine, and the Washington University, School of Medicine.

2.1. Patients

Post-HSCT patients who underwent simultaneous upper and lower endoscopies and biopsies were identified retrospectively through searches of the surgical pathology archives from each institution between 2004 and 2014. Corresponding clinical data including patient age, sex, medical history, laboratory test results, type of stem cell transplant, and follow-up information were recorded.

Only patients who had clinically confirmed acute GVHD affecting the GI tract were included in this study (105 patients; 110 cases). All patients had diarrhea at least 3 weeks posttransplant when GI mucosal injuries associated with conditioning would have improved or healed [1]. These patients could be further classified into the following categories: (i) no other known causes, such as cytomegalovirus (CMV) infection [2,15], cryptosporidium infection [6,16], or mycophenolate mofetil (MMF) treatment [17], and responded clinically to increased immunosuppression (11 patients; 12 cases), and (ii) patients with concurrent MMF treatment without recent dosing adjustment who responded to GVHD treatment (94 patients; 98 cases). Among these patients with MMF treatment, a subset (13 patients; 13 cases) also had CMV viremia but without demonstrable tissue infection, that is, no viral cytopathic effects observed on routine hematoxylin and eosin (H&E)–stained tissue sections and negative CMV immunohistochemistry stains, who responded to GVHD treatment without escalation of acyclovir therapy.

2.2. Histologic definition and grading criteria

Routine H&E-stained slides and immunohistochemical stains for CMV that had been performed on each case were reviewed.

The histopathologic features characteristic of acute GVHD affecting the intestine and stomach (Figs. 1 and 2) were the same and included epithelial cell apoptosis with sparse mononuclear inflammatory cells and rare eosinophils or neutrophils in the background in mild cases and crypt/gland loss, crypt/gland abscesses, and mucosal ulceration in severe cases [1,7–10,14]. The affected areas were the proliferative compartments which were located at the bottom of intestinal crypts (Figs. 1A and B and 2C) and in the neck regions of gastric glands (Fig. 2A) [14,18].

Because gastric acute GVHD shared the same histologic features as intestinal acute GVHD, in this study, the gastric acute GVHD was graded according to the grading system developed for acute GVHD affecting the colon. The acute GVHD lesions were classified as grades 1 to 4 (Fig. 1) based on the most commonly used system developed by Lerner et al [7] in 1974 as follows: grade 1, isolated increase in gland/crypt epithelial cell apoptosis; grade 2, epithelial cell apoptosis with isolated gland/crypt loss; grade 3, epithelial cell apoptosis with loss of contiguous glands/crypts; and grade 4, extensive gland/crypt loss with mucosal denudation [7]. Minimum criteria for increase in gland/crypt epithelial cell apoptosis were defined as more than 1 apoptotic body per biopsy piece (>1 apoptosis/piece) [18].

Esophageal involvement by acute GVHD also manifested as increased in apoptosis in the basal layer [18]. However, the grading scheme developed for colonic acute GVHD would not be applicable to squamous mucosa. Because there were no established grading criteria to classify esophageal acute GVHD, esophageal biopsies were excluded from this study. Therefore, UGI biopsy sites evaluated in this study included the stomach, duodenum, and/or proximal jejunum. LGI biopsy sites evaluated included the terminal ileum and all segments of the colon and rectum. Each patient had at least 1 biopsy from the UGI tract and 1 biopsy from the LGI tract.

When the highest histologic grade of acute GVHD among biopsies from the UGI sites was equal to the highest histologic grade of acute GVHD in biopsies from LGI sites in the same patient, the patient was classified as having comparable UGI and LGI tracts involvement, that is, lower = upper (L = U). Otherwise, the patient had GVHD affecting either LGI or UGI tract preferentially, that is, lower > upper (L > U) or lower < upper (L < U).