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Endoscopic evaluation of acute intestinal graft-versus-host disease after allogeneic hematopoietic cell transplantation

INTESTINE

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Original Article

ABSTRACT

Background/Aims: Acute graft-versus-host disease (GVHD) is a common complication of haematopoietic cell transplantation (HCT), with the gastrointestinal tract (GIT) as one of the main target organs. There is a lack of consensus regarding the site in GIT with the highest sensitivity for biopsy. The present study aimed to determine the endoscopic and histological findings in acute GVHD.

Materials and Methods: The data of 111 patients who had received allogeneic HCT were retrospectively reviewed.

Results: Allogeneic HCT was performed in 111 patients, of whom 27 (24.3%) had developed acute GVHD. Nineteen of the 111 patients with intestinal symptoms were evaluated for intestinal involvement, and 17 were diagnosed with acute intestinal GVHD. Upper endoscopic findings had a sensitivity of 64.7%, a specificity of 50%, a positive predictive value of 91.6% and a negative predictive value of 14.2%. The diagnostic accuracy of upper endoscopy was 63.1%. Lower endoscopic findings had a sensitivity of 40% and a specificity of 0%. The diagnostic accuracy of upper endoscopy with duodenal biopsy and sigmoidoscopy was 94.1%.

Conclusion: Endoscopic findings are nonspecific in acute intestinal GVHD. There is little agreement between endoscopic findings and histopathology; thus, biopsies are essential. In patients with intestinal symptoms after HCT, upper endoscopy with duodenal biopsy and sigmoidoscopy has an acceptable diagnostic yield for intestinal involvement.

Keywords: Intestinal graft-versus-host disease, endoscopy, histopathology

INTRODUCTION

Acute graft-versus-host disease (GVHD) is a common complication of haematopoietic cell transplantation (HCT). The exact incidence is unknown because of the difficulties in diagnosis. In a study including 2370 patients receiving allogeneic HCT from unrelated donors, the reported incidence of grade B or greater acute GVHD was 59% (1,2). Although the exact incidence rates are unknown, risk factors have been well established in many studies. These risk factors include the degree of human leukocyte antigen, gender disparity, transplant conditioning, prophylactic regimens and the source of haematopoietic cells (3-5).

The National Institutes of Health (NIH) consensus has classified acute GVHD into the following two subclasses based upon whether the diagnosis was made before or after 100 days: classic-acute and late-onset acute GVHD, respectively. It should be noted that the diagnosis of acute GVHD requires the absence of diagnostic or distinctive features of the chronic form and the exclusion of other possible causes, particularly infections (1).

The gastrointestinal tract (GIT) is one of the main target organs in patients with acute GVHD. In a randomized prospective study, including 110 patients with acute GVHD, the involvement rates of GIT alone or with other

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organs were 17% and 74%, respectively (6). Involvement of GIT is important for the clinician to change the immunosuppressive therapy based on its presence. Anorexia, nausea, vomiting and secretory diarrhoea with or without haematochezia are clinical symptoms of GIT involvement. The severity of GIT involvement is staged upon the severity of diarrhoea. Diarrhoea may also develop for many reasons other than acute GVHD after HCT. Therefore, a diagnosis of acute intestinal GVHD requires pathological evaluation (1). Although the diagnosis of intestinal GVHD is made by an upper and/or lower gastrointestinal system (GIS) endoscopy with biopsy, the endoscopic appearance of the affected mucosa can vary. Oedema, erythema and erosions with normal mucosa or multiple deep ulcers with or without mucosal sloughing may be observed. There are also reports of a normal endoscopic appearance with intestinal GVHD confirmed by pathological evaluation (7,8).

There is a lack of consensus regarding whether upper or lower GIS endoscopy is required first and which site has the highest sensitivity for biopsy (7,9-11). It should be noted that thrombocytopenia often prevents invasive procedures in these patients, and clinicians generally worry about associated complications. Preparing patients for colonoscopy is also a problem.

We reviewed our data of patients with allogeneic HCT to establish a standard diagnostic approach. This study aimed to determine the endoscopic and histological findings in acute GVHD with gastrointestinal symptoms.

MATERIALS AND METHODS

The data of 111 patients who had received an allogeneic HCT from September 2012 to August 2014 were retrospectively reviewed. All the patients with suspected intestinal GVHD were evaluated with upper GIS endoscopy or both upper and lower GIS endoscopy according to the presenting symptoms.

The indications for endoscopy included nausea/vomiting, hematemesis, odynophagia, ileus and diarrhoea with or without haematochezia. We performed endoscopies in 19 patients in whom a concomitant intestinal infection had been excluded by microbiological tests, including cytomegalovirus polymerase chain reaction. All 19 patients were at least 20 days post-allogeneic HCT.

The NIH criteria were used to diagnose acute GVHD with skin, liver and/or GIT biopsy according to the clinical signs and symptoms (1). The International Bone Marrow Transplant Registry (IBMTR) system was used for grading the severity of acute GVHD (12).

Endoscopic findings were staged according to the classification proposed by Cruz–Correa for upper GIS endoscopy and the Freiburg criteria for lower GIS endoscopy (Table 1, 2) (7,13). Nine patients with presenting symptoms of nausea/vomiting, hematemesis, odynophagia or ileus underwent upper GIS endoscopy, while 10 patients with a presenting symptom of diarrhoea underwent both upper and lower GIS endoscopy. All upper and lower GIS endoscopies were performed by experienced endoscopists using the same system (Olympus Evis Exera III CV-190, Olympus Europe; Hamburg, Germany).

Biopsies were taken from the duodenum, antrum and gastric body in upper GIS endoscopies and from the ileum; ascending, transverse and descending colon and rectosigmoid colon in lower GIS endoscopies. Biopsies were stained using haematoxylin–eosin and evaluated by the same experienced pathologist. The presence of apoptotic bodies, crypt/glandular abscesses and crypt/glandular destruction was considered as confirming the findings in histological specimens for the diagnosis of GVHD. The criteria proposed by Washington were used for the histological grading of acute intestinal GVHD (14).

This study was conducted in accordance with the ethical standards of the Helsinki Declaration of 1964, as revised in 2013. All study participants or their legal guardian provided informed written consent for the procedures.

Statistical analysis

Results were presented as the mean±standard deviation, median (minimum–maximum) and percentages (%). All analyses were performed with the Statistical Package for the Social Sciences 19.0 (SPSS Inc.; Chicago, IL, USA).

RESULTS

Allogeneic HCT was performed in 111 patients, of whom 27 (24.3%) developed acute GVHD as diagnosed by the NIH criteria. Among these 27 patients, 55.6% (n=15) were men and 44.4% (n=12) were women. The mean age of the patients was 45±13.8 years. The median time to diagnosis was 55 (22–110)

Table 1. Endoscopic grading for upper GIS endoscopy according to the classification proposed by Cruz–Correa (13)

Grade	Endoscopic findings
0	Normal
1	Loss of vascular pattern and/or focal moderate erythema
2	Oedema and/or diffuse moderate erythema
3	Oedema, erythema, erosions and/or bleeding
4	Ulceration, exudates and/or bleeding

GIS: gastrointestinal system

Table 2. Endoscopic grading for the terminal ileum and colon according to the "Freiburg Criteria" (7)

Grade	Endoscopic findings
1	No definite criteria
2	Spotted erythema, initial aphthous lesions
3	Aphthous lesions (Crohn-like) or focal erosions
4	Confluent defects, ulcerations, complete denudation of the mucosa

days. The underlying diseases were acute myeloid leukaemia (33.3%), acute lymphoblastic leukaemia (22.2%), myelodysplastic syndrome (18.5%), lymphoma (14.8%), chronic myeloid leukaemia (7.4%) and chronic lymphocytic leukaemia (3.7%).

Organ involvement rates were as follows: GIT only 26%, GIT and skin 14.8%, GIT and liver 7.4%, skin only 29.6%, liver only 7.4% and all organs 14.8%. The severity of acute GVHD determined by the IBMTR system and the stages of gastrointestinal involvement for the patients are summarized in Table 3.

Endoscopic findings

Nineteen patients with intestinal symptoms were evaluated for intestinal involvement either by upper GIS endoscopy alone or by both upper and lower GIS endoscopy. Presenting symptoms were as follows: diarrhoea in 10 patients, nausea/vomiting in 6 patients, hematemesis in 1 patient and odynophagia in 1 patient. In one patient with a presenting symptom of ileus, upper GIS endoscopy was performed alone.

Table 3. Demographics and clinical characteristics of 27 patients with acute GVHD

Age (mean±SD)	45±13.8
Gender (%)	
Female	44.4
Male	55.6
Time interval to diagnosis after HCT (min–max)	55 (22–110)
Organ involvement rates (%)	
GIT only	26
GIT and skin	14.8
GIT and liver	7.4
Skin only	29.6
Liver only	7.4
All	14.8
Grade of acute GVHD (%)	
A	25.9
B	48.1
C	7.4
D	18.5
Stage of intestinal involvement (%)	
0	37
1	44.4
2	11.1
3	3.7
4	3.7

HCT: haematopoietic cell transplantation; GIT: gastrointestinal tract; GVHD: graft-versus-host disease

The upper and lower endoscopic findings of 17 patients with histologically proven intestinal GVHD were graded according to the classification proposed by Cruz–Correa and the "Freiburg criteria" and are summarized in Table 4. Upper GIS endoscopic findings compatible with acute intestinal GVHD (≥grade 3) were present in 12 of 19 symptomatic patients. Upper GIS endoscopic findings had a sensitivity of 64.7%, a specificity of 50%, a positive predictive value of 91.6% and a negative predictive value of 14.2% for the diagnosis of acute intestinal GVHD. The diagnostic accuracy of upper GIS endoscopy was 63.1%.

Lower GIS endoscopic findings compatible with acute intestinal GVHD (≥grade 2) were present in only 4 of 10 patients. Lower GIS endoscopic findings had a sensitivity of 40% and a specificity of 0%.

Of all the patients with biopsy-proven intestinal GVHD, 3 patients (30%) had completely normal ileocolonoscopies and only 1 patient (5.9%) had a normal upper GIS endoscopy.

Histopathological findings

The distribution of histopathological evaluation results from different parts of GIT in patients with acute intestinal GVHD is shown in Figure 1. In 4 of 9 patients in whom upper GIS endoscopy was performed alone, only the histopathological evaluation of duodenal biopsies was compatible with intestinal GVHD. Ten patients underwent both upper and lower GIS endoscopy; the biopsy results were compatible with intestinal GVHD in 2 patients with only rectosigmoid biopsies and in 1 patient with only an ileal biopsy. The histopathological evaluation of all the biopsies from different parts of GIT was compatible with intestinal GVHD in seven patients.

Table 4. Upper and lower endoscopic findings of 17 patients with acute intestinal GVHD graded according to the classification proposed by Cruz–Correa and "Freiburg criteria" (7,13)

	n%
Upper endoscopic findings	
Grade 0	1 (5.9)
Grade 1	1 (5.9)
Grade 2	4 (23.5)
Grade 3	9 (52.9)
Grade 4	2 (11.8)
Lower endoscopic findings	
Normal	3 (30)
Grade 1	3 (30)
Grade 2	1 (10)
Grade 3	2 (20)
Grade 4	1 (10)

GVHD: graft-versus-host disease

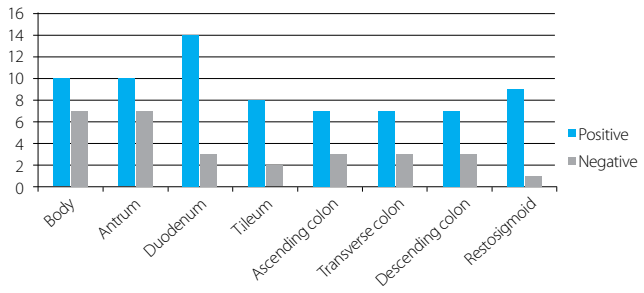

Figure 1. Distribution of histopathological evaluation results from different parts of the gastrointestinal tract in patients with acute intestinal graft-versus-host disease

DISCUSSION

Acute GVHD frequently involves GIT, and clinicians should be aware of gastrointestinal symptoms after HCT, even if they are nonspecific. Intestinal involvement is important for haematologists because histologically diagnosed acute intestinal GVHD is an indication for intensifying the immunosuppressive therapy. It is also important for gastroenterologists to decide on the most rapid and safe way to confirm a diagnosis in suspected patients.

Several reports have evaluated the endoscopic findings in acute intestinal GVHD and compared them with histopathology. The two studies by Kreisel et al. (7,15) published in 1994 and 2012 are important studies addressing the diagnostic value of lower GIS endoscopic findings in acute intestinal GVHD. In their first study, they proposed the "Freiburg criteria" for the endoscopic diagnosis of intestinal GVHD and modified it for ileocolonoscopy in the later one. In both studies, their criteria compared well with histopathological findings. Cruz–Correa et al. (13) described different criteria for grading both upper and lower GIS endoscopic findings and found agreement between endoscopic grading and histopathology. However, their findings conflict with other studies on this issue. Three different studies conducted by different groups reported little or no concordance between endoscopic findings and histopathology (9,16,17). In our study, only 4 of 10 patients in whom lower GIS endoscopy was performed and diagnosed with acute intestinal GVHD with biopsy had endoscopic grade ≥2. We found a much lower diagnostic accuracy of upper GIS endoscopy using the classification proposed by Cruz–Correa et al. (13).

Although two major studies describing endoscopic grading demonstrated a high correlation between endoscopic findings and histopathologies, the authors of both studies suggested histological evaluation of mucosal biopsies to confirm the diagnosis. In fact, the site with the highest sensitivity for biopsy remains controversial. Cox et al. (18) showed that positive rates of biopsies from the gastric region were higher than biopsies from the duodenum or rectosigmoid region in their prospective study. Ponec et al. (9) reported that a diagnosis of intestinal GVHD can be made by gastric biopsies. However, another prospective study that included data from both upper and lower GIS biopsies reported that biopsies from the distal colon had the highest sensitivity for a diagnosis (17). These results were further confirmed by Ross et al. (10) in 2008.

In the recent study by Kreisel et al. (7), the authors suggested inspecting the terminal ileum and claimed that upper GIS endoscopy may be omitted. Their results do not conflict with other reports that found the highest diagnostic accuracy of upper GIS with sigmoidoscopy. It should be noted that many clinicians still worry about the complications associated with endoscopies, particularly colonoscopies, with biopsies although it was reported that endoscopy is usually safe (9). The low performance status of patients with acute GVHD and thrombocytopenia may limit invasive procedures. Preparing patients for colonoscopies may also be problematic. It is, therefore, important to decide on a standard approach with an acceptable diagnostic accuracy for patients with gastrointestinal symptoms after HCT.

In our study, the diagnostic accuracy of upper GIS endoscopy with duodenal biopsy and sigmoidoscopy was 94.1%. Therefore, we thought that the most logical approach in suspected acute intestinal GVHD would be to perform upper GIS endoscopy with duodenal biopsy and sigmoidoscopy without bowel preparation. In cases where ileal evaluation is essential, alternative methods, including capsule endoscopy or bowel ultrasonography, can be selected (19-21).

In our study, we found that upper GIS endoscopy with duodenal biopsy was safe as previously proposed (9). Three patients had self-limiting bleeding at the biopsy site, and no patients required transfusions.

We are aware of some limitations of our study. The main limitation is its retrospective design. Compared with the largest study in the literature, we thought that it was important to evaluate the data of patients in whom upper and lower GIS endoscopies were performed and the biopsies of all segments of GIT, including the ileum, at the same time. Another issue that needs to be highlighted is that all the patients were diagnosed with acute intestinal GVHD and all were at least 20 days post-allogeneic HCT.

This study aimed to determine the endoscopic and histological findings in acute GVHD with gastrointestinal symptoms and to establish a standard diagnostic approach. We focused on the most rapid and safe way to diagnose acute intestinal GVHD. Therefore, we did not mention histological grading or compare it with other scores. A recent study reported that clinical, histological and endoscopic grading poorly correlated with each other at disease onset (22).

In conclusion, endoscopic findings are nonspecific in acute intestinal GVHD, and there is little or no agreement between endoscopic findings and histopathology. We currently require biopsies of GIT to confirm the diagnosis. We thus have to focus on non-invasive procedures or alternative methods in histopathology, such as enumeration of the duodenal Paneth cells, to provide more information regarding GVHD prognosis in the future (23).

Ethics Committee Approval: N/A.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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