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Original article

Site specific diagnostic yield of endoscopic biopsies in Gastrointestinal Graft-versus-Host Disease: A tertiary care Center experience

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ABSTRACT

Background: Gastrointestinal (GI) graft versus host disease (GVHD) occurs in up to 40% of patients undergoing allogenic hematopoietic stem cell transplantation (HSCT). However, the optimal endoscopic approach is still unclear and the area of the GI tract with the highest diagnostic yield is still a topic of debate.
Objective: We compared the diagnostic yield of different anatomic site biopsies in the diagnosis of GI GVHD and assessed the correlation of endoscopic findings with histopathology.
Methods: All cases of biopsy proven GI GVHD were obtained from pathology database AUBMC between 1/1/2005 and 31/8/2017. We retrospectively analyzed the demographical, clinical and endoscopic data.
Results: Nineteen patients were diagnosed with GI GVHD over 17.6 years. The most common presenting symptom was severe diarrhea (18 patients, 94.7%). Combining upper endoscopy and sigmoidoscopy with biopsies had the highest diagnostic yield of 90% in diagnosing GI GVHD compared to 63.6%, 78.6% and 77.8% for upper endoscopy, sigmoidoscopy and colonoscopy respectively. In macroscopically normal mucosa, the recto-sigmoid and duodenal biopsies had the highest diagnostic yield (75%). As for the macroscopically abnormal mucosa, the highest yield was for the recto-sigmoid biopsies (100%) in lower endoscopy and duodenal biopsies in the upper endoscopy (60%).
Conclusion: In a patient suspected to have GI GVHD, the best endoscopic approach is the combination of upper endoscopy and flexible sigmoidoscopy with biopsies of normal as well as abnormal mucosa. It should be emphasized that normal mucosa be biopsied especially in the duodenum and recto-sigmoid for a better diagnostic yield.

Introduction

Acute graft-versus-host disease (GVHD) after allogenic hematopoietic stem cell transplantation (allo-SCT) presents with heterogeneous symptoms involving multiple organ systems including the skin, liver and GI tract. Central to its pathogenesis are engrafted donor immune cells causing an allo-immunoreaction that leads to epithelial cell apoptosis, inflammation, and tissue injury [1]. Depending upon a number of variables associated with patients, donors, and types of transplant, the incidence of acute GVHD varies with incidence of grade II–IV GVHD at 40% in matched related donor (MRD) transplant to 50 % in matched unrelated donor (MUD) transplant [2]. GVHD has conventionally been classified into acute and chronic GVHD based on its timing from allo-SCT with a cutoff of 100 days. The current National Institute of Health (NIH) consensus definition of acute GVHD relies more on the clinical manifestations rather than the time of onset [3].

The GI tract is the second most commonly involved organ system by GVHD and is known to carry poor prognosis [3]. Clinical symptoms of GI GVHD include diarrhea, nausea, anorexia, vomiting and abdominal pain. Two phenotypes of gut GVHD: the upper and lower gut GVHD has been distinguished. These two phenotypes are hypothesized to have different presentations, natural history, prognosis and risk of mortality [4]. However, both the clinical presentation and endoscopic findings of acute GI GVHD are nonspecific. In fact, they overlap significantly with other GI

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diseases which are known to be also common in HSCT recipients. These include chemoradiation toxicity, medication side effects, or a variety of bacterial, fungal, viral and parasitic infections. At the same time, endoscopic appearance in the setting of GVHD often reveals non-specific findings or even normal mucosa [5]. Thus, the diagnosis of acute GI GVHD relies on the combination of clinical symptoms, exclusion of other causes of diarrhea and histologic evaluation of GI biopsies. The established histopathologic hallmark of acute GI GVHD is epithelial cell apoptosis [3].

Acute GI GVHD carries significant morbidity and mortality. That's why rapid diagnosis and early initiation of treatment is critical to success. Knowing that GVHD is a systemic disease, some researchers argue that GI involvement is diffuse. Thus biopsies taken from any one site will be equally efficacious in making the diagnosis as biopsies taken from multiple sites. On the other hand, others argue that GI involvement is more selective and thus taking biopsies from specific sites would be more sensitive for diagnosing GVHD [3]. Yet, the optimal endoscopic approach is still unclear and the area of the GI tract with the highest diagnostic yield is still a topic of debate [3,6].

In this retrospective study, we aim to compare the diagnostic yield of different anatomic site biopsies in the diagnosis of GI GVHD and assess the correlation of endoscopic findings with the histopathology in a series of patients in the American University of Beirut Medical Center (AUBMC), a tertiary care center

Patients and Methods

The list of all patients who underwent allo-SCT during the period between 1/1/2005 and 31/8/2017 were obtained from the SCT unit at AUBMC. All patients who underwent endoscopic evaluation after their transplantation were identified. Only patients whose biopsies were positive for GI GVHD were included (19 patients). Demographic, clinical and endoscopic data were extracted from the patients' medical records. This retrospective study was approved by the local institutional review board at AUBMC.

Upper and lower endoscopies were performed at the Endoscopy and Bronchoscopy unit at AUBMC. Endoscopy findings were grouped into five categories: normal, edema, erythema, erosions/ulcers and mucosal sloughing. As for the diagnosis and grading of GVHD, the presence of apoptosis in the absence of other inflammatory of infectious causes was the hallmark of diagnosis. Grading was based on McDonald and Sale grading system. In case any GI site was positive for GVHD, the patient was considered to have GI GVHD.

Statistical analysis

The primary outcome of our study was to find the diagnostic yield of site specific biopsies. The secondary outcome was to find the diagnostic yield of site specific biopsies on macroscopically normal or macroscopically abnormal mucosa. A histologic diagnosis of GVHD (true positive) was defined as a definitive GVHD diagnosis that was yielded by an endoscopic biopsy. A site biopsy failure was defined as the inability to detect GVHD at a specific site in a patient with a biopsy proven GVHD (false negative).

In the descriptive analysis of the sample, percentages were used for qualitative variables, and measures of central tendency (mean or median if there was great asymmetry or dispersion) and dispersion (standard deviation) were used for quantitative variables.

Results

During the study period, around 163 patients underwent allo-SCT, out of which 48 patients required endoscopic evaluation for symptoms refractory to conservative symptomatic therapy. Ultimately, only 19 patients were diagnosed with GI GVHD. The patient and transplant characteristics are listed in the Table 1. The mean age at diagnosis was 41 years (range 22–60 years). The majority of these patients had either leukemia or lymphoma as the underlying hematologic malignancy. FBATG (fludarabine, busalfan, anti-thymocyte globulin) conditioning regimen was used in 10 out of the 19 patients. The most common GI symptoms that prompted endoscopic evaluation was diarrhea (present in 94.7% of patients). Infectious causes of the diarrhea, including *Clostridium difficile*, were excluded. Less than a third of the patients had upper gastrointestinal symptoms of nausea and vomiting (26.3%). The diagnosis of GI GVHD occurred after a median of 113 days (range, 19–840). Around 47.4% of patients were less than 100 days from their transplantation. Out of 19 patients, 3 patients had a history of skin GVHD (15.8%). Data on CMV status of the recipient was available for 17 patients. All of these 17 patients were CMV seropositive. The two remaining recipient patients with unknown CMV status had donors who were CMV seropositive.

Table 2 shows the diagnostic yield of different endoscopic procedures as well as that of each biopsy site stratified by the macroscopic endoscopic appearance at each site. The yield for diagnosis of GI GVHD was nearly equivalent for sigmoidoscopy and colonoscopy (78.6 % and 77.8% respectively). The yield for upper endoscopy alone was a bit lower (63.6 %).

As for the biopsy site, the duodenum had the highest diagnostic yield (66.7%) among upper endoscopy biopsies. Regarding the lower endoscopy, the recto-sigmoid biopsies produced the highest yield (90.9%). Two patients with macroscopically normal stomach and two patients with macroscopically normal duodenum were diagnosed with GVHD microscopically at each of these sites (Table 2). Among the macroscopically normal biopsy sites in upper endoscopy, the duodenum was the best site to biopsy to produce the highest diagnostic yield (75%). Similarly, the recto-sigmoid was the anatomic site which produced the best yield in macroscopically normal mucosa (75%).

In macroscopically abnormal mucosa (edema, erythema, erosions, ulcers or mucosal sloughing), during upper and lower

Table 1
Clinical characteristics in patients with GI GVHD.

	Study Population N = 19	Control group[a] N = 25
Age (years), mean (range)	41 (22–60)	37 (21–61)
Gender (male), n (%)	15 (78.9%)	18 (72%)
Hematologic malignancy, n (%)		
Acute Lymphocytic Leukemia	2 (10.5%)	5 (20%)
Acute Myeloid Leukemia	6 (31.6%)	11 (44%)
Non Hodgkin Lymphoma	3 (15.8%)	5 (20%)
Myelodysplastic Syndrome	3 (15.8%)	0
Hodgkin Lymphoma	3 (15.8%)	0
Chronic Lymphocytic Lymphoma	1 (5.3%)	0
Aplastic anemia	1 (5.3%)	1 (4%)
Chronic Myelogenous Leukemia	0	1 (4%)
Myelofibrosis	0	1 (4%)
Dyskeratosis Congenita	0	1 (4%)
Graft type, n (%)		
Allogenic HSCT	16 (84.2 %)	18 (72%)
Haploidentical HSCT	3 (15.8 %)	7 (28%)
Time till diagnosis (days), mean (SD)	137.8 (182.4)	
Presenting symptoms, n (%)		
Diarrhea	18 (94.7%)	
Nausea/Vomiting	5 (26.3%)	
Skin lesions	4 (21.1%)	
History of Skin GVHD, n (%)	3 (15.8%)	
CMV status (n = 17)		
Positive	17	

[a] Includes patients who underwent endoscopic evaluation with biopsies negative for GVHD.

Table 2
Diagnostic yield of different biopsy sites per procedure and per endoscopic finding.

Procedure	Diagnostic yield per procedure (%)	Location	Diagnostic yield (%)	Number of patients with histologic diagnosis per macroscopic appearance		
EGD	63.6	Esophagus	33.3	+ GVHD	Normal	0
					Abnormal	1
				– GVHD	Normal	2
					Abnormal	0
		Stomach	44.4	+ GVHD	Normal	2
					Abnormal	2
				– GVHD	Normal	1
					Abnormal	4
		Duodenum	66.7	+ GVHD	Normal	3
					Abnormal	3
				– GVHD	Normal	1
					Abnormal	2
FS[a]	78.6	Recto-sigmoid	90.9	+ GVHD	Normal	3
					Abnormal	7
				– GVHD	Normal	1
					Abnormal	0
Colonoscopy	77.8	Colon	71.4	+ GVHD	Normal	0
					Abnormal	5
				– GVHD	Normal	1
					Abnormal	1
		ileum	66.7	+ GVHD	Normal	1
					Abnormal	3
				– GVHD	Normal	0
					Abnormal	2

[a] FS: Flexible sigmoidoscopy.

endoscopy, the duodenum and recto-sigmoid, were respectively the sites with the highest diagnostic yield (60% and 100% respectively)

Discussion

We have shown that biopsies performed during upper endoscopy combined with flexible sigmoidoscopy (FS) offer the highest diagnostic yield for acute GI GVHD. The study also suggests that biopsies of normal appearing mucosa are worthwhile. Our institutional approach to any patient suspected to have GI GVHD after allo-SCT is to perform endoscopic evaluation with tissue sampling. However, there is no standardized approach to either the choice of endoscopy or even the sites of sampling. Actually, these two issues are still topics of debate worldwide. Various studies, majority of which are retrospective, have evaluated the best diagnostic approach and the sensitivities of different anatomic sites. Some have found that the lower GI biopsies had the highest sensitivity in diagnosing GI GVHD [3,6,7]. Other studies reported a slightly higher sensitivity of upper GI biopsies [8,9] or nearly equivalent yields [5]. In our study, the recto-sigmoid biopsies produced the highest diagnostic yield compared to all other anatomic sites. Although it is still controversial whether GI GVHD is a diffuse or patchy disease, the lower GI was shown to be the preferential site of GI GVHD involvement in a retrospective cohort of 110 patients. The prevalence of acute GI GVHD was significantly more prevalent in the lower GI tract (90%) compared to upper GI (71%) [3]. In our study, 4 out of 9 patients (44.4%) who underwent upper and lower endoscopies had both upper and lower GI GVHD involvement. Out of these 9 patients, 2 patients with GVHD detected on upper GI biopsies could have been missed if only lower GI biopsies were obtained. Given the fact that acute GI GVHD is associated with higher morbidity and possibly mortality, prompt diagnosis is necessary.

Some studies suggested performing FS with biopsies on all patients with GI symptoms (especially diarrhea) undergoing allo-SCT. Given the small percentage of patients with isolated upper GI GVHD the authors suggest performing upper endoscopy with biopsies when FS failed to show acute GVHD [7]. Although our study showed that lower endoscopy produced higher yield than upper endoscopy (78.6% versus 63.6%), the combination of upper endoscopy and FS produced an even higher yield (90%). This was shown in a prospective study of 24 patients with acute GI GVHD post allotransplant. Flexible sigmoidoscopy with EGD was equally sensitive in diagnosing GVHD as colonoscopy with terminal ileal intubation (94%). These two endoscopic approaches produced higher positive rates compared to either EGD or flexible sigmoidoscopy (76 and 82 % respectively) [6].

With respect to lower endoscopy, our results show that flexible sigmoidoscopy and colonoscopy produced similar diagnostic yield (78.6 and 77.8% respectively). These results are in parallel with previous studies where sensitivities of right and left sides of the colon were comparable [6,7,10]. A large cohort of 105 patients surveyed the entire lower GI tract with biopsies and showed that acute GI GVHD to be equally prevalent in various regions of the lower GI tract. Thus recto-sigmoid biopsies obtained through FS without colonoscopy are sufficient representative of lower GI biopsies [7]. Flexible sigmoidoscopy is a simple procedure that does not require colonic preparation which is an advantage in this population of patients. Upper endoscopy is a fast procedure and requires minimal doses of conscious sedatives. This can be translated into institutional approach whereby flexible endoscopy and EGD with biopsies be the initial endoscopic evaluation in a patient with suspected acute GI GVHD.

As for upper endoscopy, there is reported variation between different biopsy sites in upper endoscopy. Similar to Ip et al, our study results showed that the duodenum produced the higher yield (66.7%) in diagnosing GI GVHD among biopsy sites. Duodenal and gastric biopsies are not always concordant in diagnosing GVHD [11]. In our 19 patient cohort, 10 patients underwent upper endoscopy with gastric and duodenal biopsies. There was around 80% concordance (8 patients) between both biopsy sites which is a bit higher than the reported concordance in other studies [9,10]. For this reason, it's recommended that whenever upper endoscopy is performed, both gastric and duodenum biopsies be obtained.

Endoscopic macroscopic findings are often normal or even nonspecific. Around 50% of gastric and duodenal biopsy proven GVHD had normal mucosal appearance on endoscopy. Out of 10

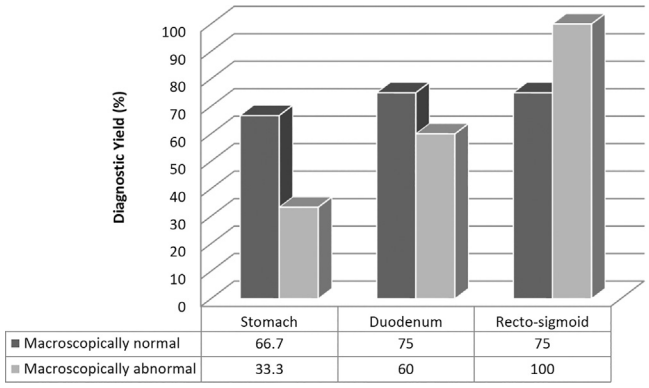

Fig. 1. Diagnostic yield of each biopsy site according to endoscopic appearance.

patients with recto-sigmoid GVHD, three patients had normal endoscopic findings. Biopsy proven GVHD was diagnosed in all cases when rectosigmoid was macroscopically abnormal (Fig. 1). Nonspecific findings like edema, erythema and even small erosions are more commonly seen. In upper endoscopy, these nonspecific features might reflect either chronic Helicobacter pylori related gastritis or even medication or chemotherapy induced gastropathy. Nomura et al. examined 115 subjects and found that gastric mucosal exfoliation, although a rare endoscopic finding, has a specificity and PPV of 100% [12]. The observation that GVHD can still be diagnosed despite normal endoscopic appearance advocates the need to biopsy both normal and abnormal gastric, duodenal as well as rectosigmoid anatomic sites.

Over the last two decades, many studies assessed the role of non-invasive modalities in acute GI GVHD diagnosis. Of interest are the wireless video-capsule endoscopy (WCE) and the probe-based confocal laser endomicroscopy (pCLE) [13]. One of the early studies addressing the role of WCE was carried out evaluated WCE in 10 patients with suspected acute GI GVHD [14]. Along with other studies, this study stressed the high negative predictive value (NPV) of WCE [13,14]. All these studies, however, were limited by the very low number of patients recruited. Moreover, although WCE can evaluate the small bowel mucosa, which is accessible to neither upper endoscopy nor colonoscopy, it is reported to have low specificity. As noted earlier, acute GI GVHD has nonspecific mucosal lesions. Thus, any small bowel lesion detected on WCE should be interpreted with caution. For instance, it is reported that small bowel ulceration detected on WCE could be attributed to CMV infection in patients after allo-SCT [15]. pCLE's role in acute GI GVHD diagnosis is still under investigation. Data, so far, shows promising results with high sensitivity and specificity. Of course, additional data is needed to confirm these results [13]. Despite all these advances, histopathology remains the gold standard for the diagnosis of acute GI GVHD [3].

The major limitation of this study is its retrospective nature. The small number of patients, as well as the absence of a standard biopsy protocol makes our data analysis very limited.

In conclusion, all patients with suspected GI GVHD should be evaluated by endoscopy and tissue sampling. Our study supports the combination of upper endoscopy and flexible sigmoidoscopy as the best initial endoscopic approach. In order to increase the diagnostic yield of endoscopy, all three sites including the stomach, duodenum and rectosigmoid should be biopsied. Normal endoscopic mucosal appearance does not exclude the diagnosis. That's why it should be emphasized to biopsy both normal and abnormal mucosa for the sake of prompt diagnosis of GI GVHD.

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