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Gastrointestinal Involvement in Chronic Graft-versus-Host Disease: A Clinicopathologic Study

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ABSTRACT

The original histopathologic description of chronic graft-versus-host disease (CGVHD) of the gastrointestinal (GI) tract was from autopsy series. There is little information on the evaluation of living patients with CGVHD and GI symptoms. We reviewed data on 40 consecutive patients with CGVHD and persistent GI symptoms who underwent endoscopic examinations. The diagnosis of CGVHD in these 40 patients was made on the basis of clinical criteria and confirmed by histology of other involved organs in 70%. Patients had progressive (in 19 patients, or 48%), quiescent (in 11, or 27%) or de novo–type (in 10, or 25%) onset of their CGVHD. Four groups were defined based on the following histologic criteria: (1) consistent with acute GI GVHD if there was marked apoptosis with or without cryptitis, (2) suggestive of acute GI GVHD if there was scattered apoptosis with or without cryptitis, (3) suggestive of chronic GI GVHD if there were at least 2 histologic indicators of chronicity such as fibrosis and significant crypt distortion, and (4) no histologic evidence of GVHD. Results of microbiologic, radiologic, and malabsorption studies, if performed, were also retrieved. Median time from diagnosis of CGVHD to GI endoscopy was 4.5 months (0-109 months). The major GI symptoms at the time of endoscopy were diarrhea, abdominal pain/cramping, nausea/vomiting, weight loss, dysphagia, and early satiety. The endoscopic examination was nonspecific for the diagnosis of GI GVHD except for diffuse mucosal sloughing. Based on the histologic criteria in 22 patients with biopsies, 13 cases (59%) were considered to have acute GI GVHD, and 3 cases (14%) were felt to show possible chronic GI GVHD; changes of both acute and chronic GVHD were seen in 6 (27%) cases. GI dysmotility was diagnosed in 7 (18%) patients, including 2 of the patients who had histologic changes suggestive of chronic GVHD. Other causes of the GI symptoms included infection, drug side effect, and malabsorption. In conclusion, GI involvement by acute GVHD appears to be a major cause of persistent GI symptoms in patients with chronic GVHD. An isolated form of chronic GI GVHD confirmed by histology is an uncommon phenomenon in the actual clinical setting.

KEY WORDS

Chronic • Graft-versus-host disease (GVHD) • Intestinal • Gut • Pathology

INTRODUCTION

Since the use of modern immunosuppressive treatment regimens began, there has been a considerable shift in the pattern and clinical manifestations of chronic graft-versus-host disease (CGVHD). Many of the severe manifestations of the disease reported in the initial description of CGVHD [1,2], such as nasal mucosal CGVHD, arthralgia/arthritis, serositis, myositis, and cardiopulmonary involvement, are rarely seen. One of the controversial sites of involvement in CGVHD is the gastrointestinal (GI) tract. Although intestinal involvement in patients with untreated CGVHD was described in early studies [1,2], this is now rarely seen with the reported symptoms and radiographic and histologic findings.

In clinical practice, however, physicians are often faced with CGVHD patients who also have a variety of GI symptoms such as esophageal reflux, dysphagia, bloating, weight loss, and diarrhea [3,4]. These GI symptoms are often attributed to gastrointestinal involvement by chronic GVHD. However, there has

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been no consensus as to the clinical symptoms or histologic findings of GI CGVHD. Although rectal biopsy is known to have diagnostic utility, using the crypt abscess as a major diagnostic criterion in acute GVHD [2], there is no established role of endoscopic evaluation and mucosal biopsy in the diagnosis of chronic GI GVHD. The histologic changes of chronic GI GVHD (ie, fibrosis, mononuclear cell infiltration, and sclerosis and hyalinization of small venules) are mainly confined to submucosa and subserosa [5,6]. There is a need to improve the current understanding of GI involvement in CGVHD. In this case series, we describe our clinical findings in a group of patients with chronic GVHD whose GI symptoms required endoscopic evaluation.

PATIENTS AND METHODS

Data on 40 consecutive patients with CGVHD who underwent 42 upper and/or lower GI endoscopies because of persistent GI symptoms were reviewed. Patients included in this study were selected based on their history of endoscopic evaluation and the availability of GI pathology reports between 1987 and 2000. Endoscopic examinations of 28 cases were performed by a single gastroenterologist at the Johns Hopkins Hospital. The remaining 14 examinations were done by other gastroenterologists. The site of the GI tract to be examined by endoscopy was determined primarily by the patients' main symptoms. If a patient had only diarrhea, upper GI endoscopy was not included in the evaluation process. If a patient had both upper and lower GI symptoms, both sites of the GI tract were examined. Results of other diagnostic evaluations including microbiologic, radiologic, and malabsorption studies, if performed, were retrieved. Six additional patients were not included in the study because of inadequate biopsies (lacking submucosa or adequate tissue for interpretation). Sixteen (40%) patients underwent transplantation in outside institutions and were referred to Johns Hopkins for the management of chronic GVHD. All patients were diagnosed with chronic GVHD of the skin, eye, mouth, or liver based on established clinical and histologic criteria [1,7-9] prior to (n=29) or at the onset of (n=11) GI symptoms. In 28 patients (70%), the diagnosis of CGVHD had been confirmed by histologic evaluation of the skin or liver, or both.

All biopsy slides had been previously read and reported by GI pathologists at Johns Hopkins. One third of these slides were from outside institutions. For this particular study, the pathology was reviewed blindly by a different GI pathologist (M. T.). The pathology was reviewed without clinical information to as much as possible prevent bias in the interpretation. Four groups were defined based on histologic criteria: (1) features consistent with acute GI GVHD if there was marked apoptosis with or without cryptitis (Figure 1A,B); (2) features suggestive of acute GVHD such as scattered apoptosis with or without cryptitis; (3) features suggestive of chronic GI GVHD if there were at least 2 histologic indicators for chronicity, such as fibrosis, significant mucosal architectural (crypt) distortion (Figure 1C), increased lymphocyte/plasma cell infiltration in the lamina propria, and the presence of Paneth cell metaplasia (defined by Paneth cells in the left colon and/or rectum, which are normally present in the right and transverse colon) (Figure 1D) or pyloric metaplasia; and (4) no evidence of GVHD. Other diagnostic evaluations included microbiologic studies, a 24-hour fecal fat excretion, computed tomography and upper GI series, cineesophagogram. The outcome of the GI symptoms and related findings after the endoscopic evaluation were noted.

In general, occasional or scattered apoptic bodies would equate to 1 to 2 apoptotic bodies per 5 crypts. In many of the specimens, a spectrum of changes between normal mucosa (no GVHD) and cryptitis/crypt abscess was reported. Invasion of crypt epithelium by neutrophils, or *cryptitis*, was used as an indicator of acute inflammation.

The crypt abscess was defined as a crypt that is dilated and contains necrotic cellular debris with inflammatory cells (neutrophils, eosinophils, or mononuclear cells) in the lumen. These features, in combination with apoptosis, were consistent with acute GI GVHD. When these features were present to a lesser degree, we categorized this as suggestive of acute GVHD. There were various histologic features indicating chronicity or chronic inflammation, which included fibrosis or scarring, lymphoplasmacytic infiltration in lamina propria, architectural (crypt) distortion or loss, submucosal fibrosis, Paneth cell metaplasia, pyloric metaplasia, and inflammatory polyp formation. Architectural distortion was defined by forked crypts and/or Paneth cell metaplasia (left colon and rectum), crypt loss and/or crypt shortfall (crypts no longer extend to muscularis mucosae), gland loss (if biopsy from the body) and/or intestinal metaplasia (body or antrum), villous blunting, pyloric metaplasia, and gland distortion (duodenum). Chronic *Helicobacter pylori* infection also causes intestinal metaplasia, and *H pylori* infection was therefore sought. Two patients were found to have *H pylori* infection.

RESULTS

Forty consecutive patients with chronic GVHD underwent a total of 42 upper (n=14), lower (n=15) and both upper and lower (n=13) GI endoscopic examinations between January 1987 and November 2000. Demographic features and bone marrow transplantation (BMT) and GVHD data are summarized in Table 1. There were 27 male patients and 13 female patients, with a median age of 31.5 years (range 1 to 52). Thirty-one patients developed acute GVHD following the transplantation with 80% of those having grade 2-4 acute GVHD. Of those with GVHD, 10 (32%) patients had gut involvement. Of the 10 with acute GI GVHD, 5 had persistent GI symptoms at the time of referral and evaluation for chronic GVHD. For the entire group, the median time from the transplantation to diagnosis of CGVHD was 5 months (2-21 mos). The diagnosis of chronic GVHD was made before day +100 in 9 (22%) patients. Nineteen (48%) patients had progressive onset of chronic GVHD, 11 (27%) had quiescent onset, and 10 (25%) had de novo–type onset.

The major GI symptoms at the time of endoscopic evaluation included diarrhea (74%), abdominal pain/cramping (45%), nausea/vomiting (33%), and weight loss (19%). The diarrhea was severe (> 1 liter or ≥5 times/day) in 48% of the patients. Median time from diagnosis of CGVHD to GI endoscopy was 4.5 months (0-109 months). Eleven patients (26%) had their GI evaluation done at the time of their initial diagnosis of chronic GVHD (Table 2).

The patients were subdivided by the time after diagnosis of CGVHD. The clinical presentation and histologic findings in the 25 patients who developed GI symptoms within 1 year of diagnosis of CGVHD were different from the late-onset (> 1 year) group. Many of these patients had progressive onset of

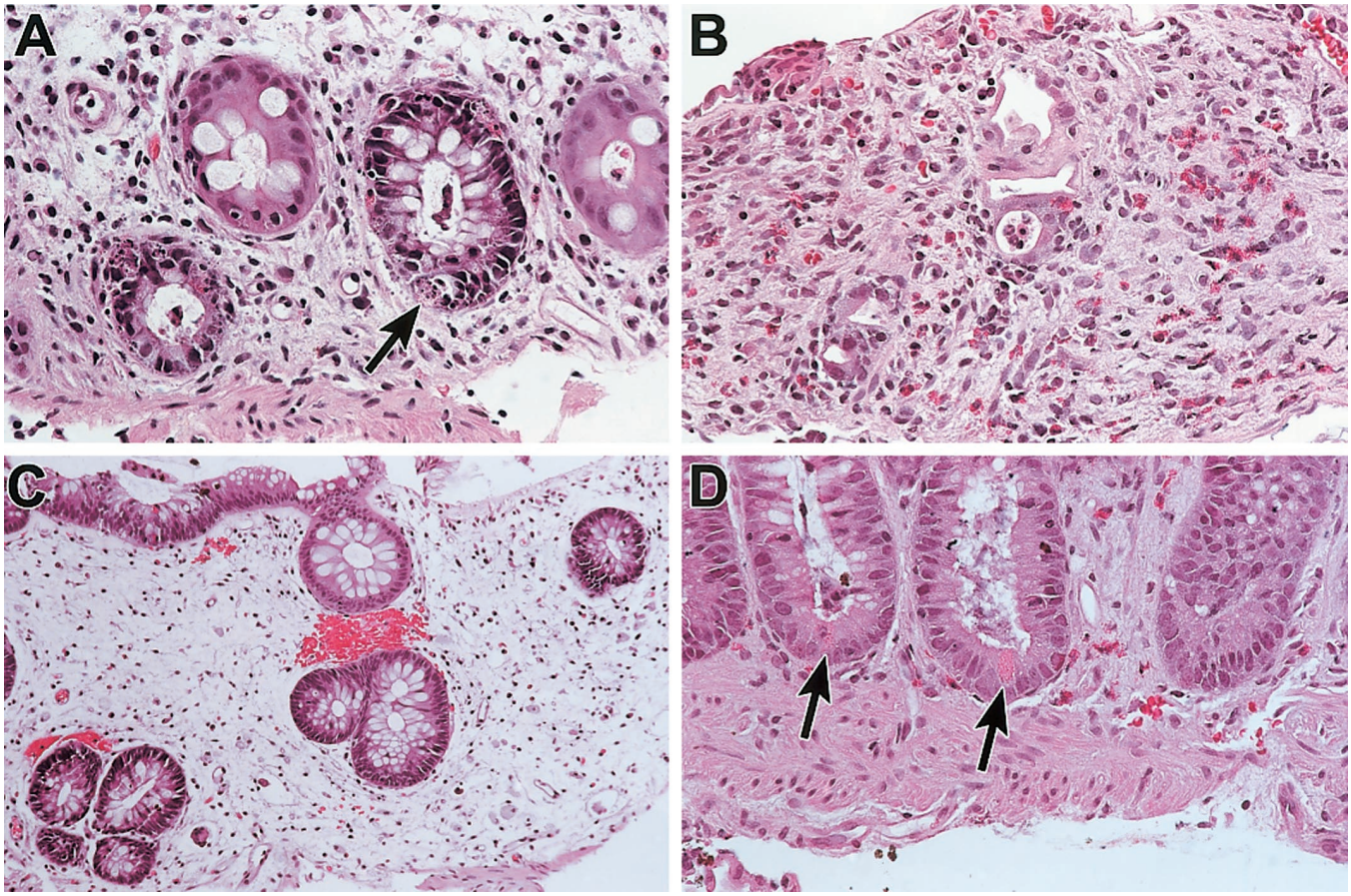

Figure 1. Histologic changes of acute and chronic graft-versus-host disease (GVHD) in the colon. A, numerous apoptotic bodies are present in the crypt epithelium (arrow), consistent with acute GVHD. B, Several crypts are present with marked damage and reactive epithelial changes as well as neutrophils in the lumen of the central crypt (cryptitis), changes consistent with acute GVHD. C, Marked crypt distortion and loss is present in this biopsy specimen, suggesting chronic GVHD. D, Paneth cell metaplasia (arrows) is another marker on chronic inflammatory disease that is suggestive of chronic GVHD in the right clinicopathologic setting.

CGVHD with persistent symptoms of acute GI GVHD. Thus symptoms of diarrhea, abdominal pain/cramps, and nausea/vomiting were more common in this early-onset group. All 22 patients who had acute GVHD features in biopsy samples were in this early-onset group. Also, all 7 patients who had GI infections (*Clostridium difficile* [n=2], CMV [n=1], bacterial overgrowth [n=2] and *Helicobacter pylori* [n=2]) were in this early-onset group. Not surprisingly, the 12 patients who expired during the course of follow-up were in this early-onset group.

In the 15 (35%) patients who underwent endoscopy for GI symptoms more than 1 year after the diagnosis of chronic GVHD, chronic diarrhea (n=9), weight loss (n=6), abdominal pain (n=5), and dysphagia (n=4) were the most common GI symptoms. Histologic findings of GI GVHD were found in only 3 (20%) patients. The most frequent diagnoses in this subgroup were drug-induced gastritis (33%), GI dysmotility (27%), and pancreatic insufficiency responding to pancreatic enzyme replacement therapy (13%). These patients improved their symptoms with therapy directed at the underlying cause, such as discontinuing the drug that was causing the gastritis, starting pro-motility agents, and replacing pancreatic enzymes.

Except in patients with diffuse mucosal sloughing, there were no pathognomonic endoscopic findings for GVHD. Based on histopathologic criteria we used, 22 (52%) of 42 biopsies were considered to be consistent with GI involvement by acute GVHD in 13 (59%), possible chronic GVHD in 3 (14%), and both in 6 (27%) cases. Characteristics of the 9 cases that had a component of possible chronic GVHD involvement in the GI tract are summarized in Table 3.

GI dysmotility, including gastroparesis, esophageal spasm, and delay in transit time was diagnosed in 7 patients. Four (57%) were in the late-onset GI GVHD group. Drugs such as mycophenolate mofetil, clofazimine, and non-steroidal anti-inflammatory agents were felt to be the cause of GI symptoms in 6 cases, 5 of which (83%) were in the group of late-onset GI GVHD.

All patients were managed according to the underlying cause of GI symptoms. Patients who were diagnosed with active GVHD of the GI tract were treated with immunosuppression. Drug-related or infectious causes were treated accordingly. Overall, the GI symptoms either resolved or improved in 36 cases (86%) with appropriate management.

As of December 2001, 12 of 22 patients who had GI GVHD expired; 11 of these deaths were due to non-relapse causes. Prolonged acute GVHD in the intestinal tract was associated with adverse outcome; all 5 patients in this category died.

Table 1. *Patient Characteristics*

Male/female	27/13
Median age, y (range)	31.5 (1-52)
BMT data	
Bone marrow was the source of graft	40 (100%)
Second BMT/DLI/"mini" BMT	1/1/1
Matched-related donor	33 (82%)
Matched-unrelated donor	5 (12%)
Mismatched-related donor	2 (5%)
Cytoreductive therapy	
Cyclophosphamide and TBI	19 (48%)
Busulfan and cyclophosphamide	17 (42%)
Others	4 (10%)
Acute GVHD	31 (77%)
Grade 1	6 (20%)
Grade 2	24 (77%)
Grade 3-4	1 (3%)
Skin involvement	30 (97%)
Liver involvement	11 (35%)
Gut involvement	10 (32%)
Diagnosis of CGVHD	Between 1/1987 and 11/2000
Before 1995	18
1995 or later	22
Median time to diagnosis of CGVHD (range)	5 months (2-21)
Type of presentation of CGVHD	
De novo	10 (25%)
Quiescent	11 (27%)
Progressive	19 (48%)
Major organ involvement at diagnosis of CGVHD	
Skin	36 (90%)
Oral	18 (45%)
Liver	15 (38%)
Eye	9 (22%)
Gut	7 (17%)

DLI indicates donor lymphocyte infusion.

DISCUSSION

Our data in this study suggest that persistent GI symptoms occurring during the course of chronic GVHD are due to GVHD itself in 55% of the cases, as evaluated with endoscopy. However, the histopathologic changes were consistent with acute GVHD in the majority of patients who had biopsy-proven GVHD. All 5 patients with persistent acute GI GVHD died, although the number of cases included in this series did not allow us to perform a meaningful risk factor analysis,

In the present study, we used a stringent definition of chronic GI GVHD to avoid introducing bias and inter-observer variation. The most important diagnostic criterion for the evidence of acute GVHD in the GI tract is the demonstration of epithelial single cell necrosis (apoptosis), which may be accompanied by increased inflammation (cryptitis) and reactive epithelial changes or loss [5,10]. Our criteria for diagnosing acute GI GVHD in patients with chronic GVHD conform to this definition. In contrast, many transplant physicians categorize GVHD by day post-BMT rather than by biologic and histologic changes. GVHD is usually called chronic if it is diagnosed after day 100 of transplant. In our cohort, the diagnosis of chronic GVHD was made before day 100 in 9 (22%) patients based on the clinical features, including lichenoid skin rash; lichenoid changes in oral mucosa; development of dry mouth and/or dry eye; and persistent cholestatic liver abnormalities plus histologic criteria of chronic GVHD on skin, oral, and liver biopsies, which include sclerosis, epidermal keratosis, vacualization, li-

Table 2. *Evaluation of GI Symptoms*

GI symptoms (n = 42)	
Diarrhea	31 (74%)
Abdominal pain/cramps	19 (45%)
Nausea/vomiting	14 (33%)
Weight loss	8 (19%)
GI bleeding	5 (12%)
Dysphagia	5 (12%)
Early satiety/fullness	5 (12%)
Heartburn	2 (5%)
Failure to thrive	1 (2%)
Partial intestinal obstruction	1 (2%)
Median time from diagnosis of CGVHD to GI biopsy, range (n = 42)	4.5 months (0-109)
Biopsy at initial diagnosis of CGVHD	11 patients (26%)
Biopsy within 1 month after diagnosis of CGVHD	17 patients (40%)
Biopsy within 1 year after diagnosis of CGVHD	30 patients (71%)
Biopsy after 3 years of diagnosis of CGVHD	6 patients (14%)
On systemic immunosuppression at GI presentation	39 (93%)
Immunosuppressive medication at GI evaluation (n = 39)	
Corticosteroid	21 (54%)
Cyclosporine	16 (41%)
Tacrolimus (FK-506)	15 (38%)
Mycophenolate mofetil	10 (26%)
Thalidomide	5 (13%)
Azathioprine	4 (10%)
Daclizumab	2 (5%)
Pentostatin	1 (3%)
GI sites evaluated (n = 42)	
Colon and rectum	27 (64%)
Small bowel	23 (55%)
Esophagus	16 (38%)
Stomach	13 (31%)
GI biopsy site (n = 42)	
Upper GI	14 (33%)
Lower GI	15 (36%)
Both upper and lower GI	13 (31%)
Severity of diarrhea (n = 31)	
Mild (≤0.5 L or <3 times/day)	4 (13%)
Moderate (0.5-1.0 L or 3-5 times/day)	12 (39%)
Severe (>1 L or >5 times/day)	15 (48%)
Other diagnostic work-up (positive/all results)	
Infectious	7/41
C difficile	2/41
CMV	2/41
Bacterial overgrowth	2/41
H pylori	1/41
CT/GI series (thickened, dilated, featureless small bowel)	6/8
Cineesophagogram (stricture, dysmotility, gastroparesis)	5/9
24-hour fecal fat	3/4
Abdominal X-ray (ileus)	1
Surgical exploration (fibrotic gall bladder)	1

CMV indicates cytomegalovirus.

Table 3. *Description of 9 Cases with Possible Chronic GI GVHD*

Case	GI Symptoms	Major Endoscopic Findings	Histologic Criteria for GI GVHD	Other Tests	Type of GI GVHD	Time from CGVHD to GI GVHD (mos)
1	Diarrhea	Erythema (rectum)	Crypt distortion, Paneth cell metaplasia	No infection	Possible chronic	11
2	Abdominal pain, diarrhea, GI bleeding, partial obstruction	Erythema, edema, cobblestone, granular, friable, mucosa and a bleeding site (duodenum), edema, markedly friable mucosa, erosions (colon and rectum)	Crypt apoptosis, Crypt distortion and drop out, fibrosis	No infection CT: thickened bowel	Definite acute and possible chronic	0.7
3	Chronic diarrhea and weight loss	Nonspecific findings (stomach, duodenum, colon and rectum)	Active chronic inflammation, Paneth cell metaplasia, crypt distortion	No infection	Possible chronic	12
4	Chronic diarrhea and weight loss	Granular edematous mucosa (duodenum, jejunum), normal (rectum)	Chronic inflammation, villous blunting, focal cryptitis scattered apoptosis	No infection CT: dilated featureless small bowel. Fecal fat: 10 g/day	Possible acute and possible chronic	8
5	Nausea, vomiting and diarrhea	No info—upper and lower GI endoscopy	Focal epithelial cell necrosis, lymphocyte satellitosis, focal apoptosis, crypt drop out and distortion	CMV (+)	Definite acute and possible chronic	0
6	Rectal bleeding and diarrhea	Mucosal granularity (rectum), normal (stomach and duodenum)	Mucosal ulcers, Crypt distortion, Scarring of lamina propria, lymphocyte depletion of lamina propria, occasional apoptotic cells	No infection upper GI series: Multiple abnormal ileal loops, featureless small bowel, fine nodularity, esophageal spasm and delay in transit to colon	Possible acute and possible chronic	1
7	Nausea, vomiting, diarrhea, GI bleeding	No info—lower GI endoscopy	Apoptotic lesions, crypt distortion and loss, increased plasma cells in lamina propria (colon and rectum)	No infection CT: thickened bowel wall and ascitis	Definite acute and possible chronic	0
8	Abdominal pain, diarrhea, GI bleeding	No info—lower GI endoscopy	Active inflammatory disease, cryptitis and crypt abscess, scattered apoptosis, crypt distortion Scarring	No infection	Definite acute possible chronic	0
9	Diarrhea	No info—lower GI endoscopy	Fibrosis, crypt distortion	No infection	Possible chronic	27

chen planus-like histology, varying degrees of dermal lymphocyte infiltration with or without epithelial apoptotic elements, and cryptitis. The diagnostic criteria we used for chronic GI GVHD was devised by us because almost all the data about chronic GI GVHD were based on autopsy studies that were reported before there was early recognition and treatment of chronic GVHD. Nonetheless, at least 2 histologic indicators of chronic inflammation should be sufficient to suggest the presence of chronic GVHD component in the intestinal lesions of these patients.

There may be several plausible explanations for the relative uncertainty and infrequency of chronic GI GVHD in this patient population. First, almost half of the study subjects in this report had progressive onset of CGVHD. In this setting, it is not surprising to observe ongoing acute GVHD features in GI histology. Second, using definitions in the literature, diagnosing chronic GI GVHD is difficult. The symptoms are relatively nonspecific, there are no specific endoscopic findings, and mucosal biopsies may miss deep fibrosis or inflammation. Autopsy series have shown that the histologic hallmark of the presence of an inflammatory process is usually located in the deep submucosal and subserosal layers of the GI wall [5,6]. Although deeper biopsy sampling may increase the yield of capturing chronic GI GVHD, this is not an acceptable approach because of the potential risks associated with it. Also, the optimum location for obtaining a biopsy could be missed, and this may result in underestimation of severity of GVHD or even missing the diagnosis of GVHD. In a recent report, Ponec et al suggested both the endoscopic evaluation and the histology of the upper gut can underestimate the severity of acute GVHD elsewhere in the intestine unless extensive mucosal sloughing is seen [11]. Finally, chronic GI GVHD may actually be rare. The GI symptoms of about one third of the patients in this study were caused by something other than GVHD.

The diagnosis of GI involvement by GVHD requires extensive evaluation to rule out other causes of GI symptoms. In

patients within a year of diagnosis of chronic GVHD, ongoing acute GVHD and infection were the most common causes of the GI symptoms. In patients more than a year from the original diagnosis of chronic GVHD, drug-induced gastritis, GI dysmotility, and pancreatic insufficiency responding to pancreatic enzyme replacement therapy were the most common causes of GI symptoms, not GVHD. It is not clear whether motility disorders are part of chronic GVHD because the histology in the majority of these patients failed to show pathologic findings. In 7 patients in this series, gastroparesis, esophageal spasm, and delay in transit were found. Only 2 of these patients met the histologic criteria for possible chronic GI GVHD. Gastroparesis was described as a motility disorder after BMT. In a recent study, 14 of 18 patients who underwent BMT had delayed gastric emptying, mostly responsive to prokinetic agents [12]. Nine of these patients were also evaluated with upper GI endoscopy. GVHD on gastric biopsy was an uncommon finding and was mild when present. Seven patients in the present study had GI motility disorder with or without associated GI GVHD. Barium swallow studies done in these patients demonstrated esophageal dysmotility/spasm, overall delay in transit time, and gastroparesis.

Weight loss was one of the common symptoms associated with chronic diarrhea in our patients. Although poor oral caloric intake is certainly one of the possible causes of weight loss in patients with CGVHD, it is not the only one. The cause of weight loss remains obscure in some of these patients. In our routine GVHD practice, we have seen many cachectic patients despite adequate oral intake [13]. After ruling out an active inflammatory process in the GI tract or a motility disorder, increased expression and translation of various hormones and cytokines (tumor necrosis factor-alpha) may be the cause of weight loss in patients with chronic GVHD. A recent study suggested that patients with chronic extensive GVHD show an increase in resting energy expenditure and alterations in fat and carbohydrate oxidation rates. These changes seemed to be the result of increased action of glucagon and norepinephrine [14]. The role of TNF-alpha in the mechanism of weight loss in chronic GVHD is not well known. In a murine study, transgenic mice that overexpress TNF-alpha gene were created. These mice had severe cachexia and skin changes that resembled GVHD [15].

The other causes of GI symptoms as shown in this series included drug side effect, infections, and gastroesophageal reflux disease/gastritis. It is important to remember this differential diagnosis because the symptoms quickly resolve when the underlying causes are identified and eliminated. We diagnosed malabsorption in 3 patients based on history, clinical findings, and increased 24-hour fecal fat excretion. They responded well to pancreatic enzyme replacement therapy with significant improvement in their abdominal pain and diarrhea. As we reported recently [16], pancreatic insufficiency should be in differential diagnoses in patients with CGVHD who have had a longstanding history of bulky, oily, and foul-smelling diarrhea.

Although we included a substantial number of patients who were evaluated both clinically and pathologically in the present study, we cannot state with certainty that the results are reflective of all patients with GI GVHD. Given the lack of consensus in the definition of chronic GI GVHD, we believe our data will provide important information on causes of GI symptoms in late-posttransplantation patients. In conclusion, patients with GI acute GVHD may have persistent acute GI GVHD even though clinically their skin and other organs now appear to be consistent with chronic GVHD. Patients with persistent acute GI GVHD have a very poor prognosis. In this series, all died of GVHD and its complications. Although chronic GVHD itself may involve the GI tract, it is a rare phenomenon, is difficult to diagnose, and is seldom seen without simultaneous acute GVHD.

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