ORIGINAL ARTICLE

Severe Acute Gastrointestinal Graft-vs-Host Disease

An Emerging Surgical Dilemma in Contemporary Cancer Care

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Objective: To determine the natural history of and guidelines for the surgical management of severe acute gastrointestinal (GI) graft-vs-host disease (GVHD) after allogeneic hematopoietic stem cell transplantation (HSCT).

Design: Case series from a prospective database.

Setting: Tertiary care referral center/National Cancer Institute–designated Comprehensive Cancer Center.

Patients: A total of 63 of 2065 patients (3%) undergoing HSCT for hematologic malignancies from February 1997 to March 2005 diagnosed clinically with severe (stage 3 or 4) acute GI GVHD.

Main Outcome Measure: Percutaneous or surgical intervention. Perforation, obstruction, ischemia, hemorrhage, and abscess were considered surgically correctable problems.

Results: Severe acute GI GVHD was diagnosed in 63 patients (median age at HSCT, 47.6 years) at a median of 23 days after HSCT. Clinical diagnosis was confirmed histologically in 84% of patients. On computed tomography and/or magnetic resonance images, 64% had bowel wall thickening, 20% had a normal-appearing bowel, and 16% had nonspecific findings; none had evidence of perforation, obstruction, or abscess. All were initially treated with immunosuppression. Only 1 patient (1.6%) required intervention, undergoing a nontherapeutic laparotomy for worsening abdominal pain. A total of 83% of patients have died (median time to death from HSCT, 119 days; from GI GVHD diagnosis, 85 days). None who underwent an autopsy died of a surgically correctable cause.

Conclusions: This series represents a large single-center experience with GI GVHD reviewed from a surgical perspective. Operative intervention was rarely required. Therefore, mature surgical judgment is necessary to confirm the absence of surgically reversible problems, thus avoiding unnecessary operations in this challenging patient population.

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ALLOGENEIC HEMATOPOIetic stem cell transplantation (HSCT) is an evolving technology in cancer therapeutics. Patients with a variety of hematologic malignancies are treated with myeloablative or immunosuppressive chemotherapy with or without radiation therapy, followed by the infusion of allogeneic stem cells. One of the most important complications associated with this increasingly common treatment is acute graft-vs-host disease (GVHD), the immunologic attack of transplanted donor T lymphocytes against foreign host tissues.[1]

See Invited Critique at end of article

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The skin, liver, and gastrointestinal (GI) tract are the main targets of acute GVHD.[1-3] The first and most common clinical manifestation of acute GVHD is often a pruritic maculopapular skin rash.[1] The liver is the second most commonly involved organ.[4] Acute GVHD of the liver presents with hyperbilirubinemia and increases in alkaline phosphatase and, to a lesser degree, transaminase levels.[3] Hepatic failure with encephalopathy is unusual unless GVHD is long-standing.[1] Gastrointestinal tract involvement is less common but is frequently the most severe and difficult to treat.[1] While skin or liver GVHD rarely necessitate surgical management, the symptoms of acute GI GVHD may be concerning enough to warrant, at minimum, a surgical evaluation.[5]

Acute GVHD occurs after 35% to 40% of transplants from related donors and 40% to 50% of transplants from unrelated individuals.[6-8] The clinical stage of acute GVHD is determined independently for

Table 1. Organ Staging of GVHD[9]

Stage	Symptoms: Skin	Symptoms: Liver, Bilirubin Level, mg/dL	Symptoms: GI Tract[a]
0	No rash due to GVHD	<2	<500 mL/d of diarrhea (5 mL/kg for patients younger than 12 y)
1	Maculopapular rash on <25% of body surface[b]	2-3[c]	500-999 mL/d of diarrhea (5.1-10 mL/kg for patients younger than 12 y) or persistent nausea with histologic evidence of GVHD in the stomach or duodenum
2	Maculopapular rash on 25%-50% of body surface[b]	3.1-6.0[c]	1000-1499 mL/d of diarrhea (10.1-15.0 mL/kg for patients younger than 12 y)
3	Maculopapular rash on >50% of body surface[b]	6.1-15.0[c]	≥1500 mL/d of diarrhea (>15.0 mL/kg for patients younger than 12 y)
4	Generalized erythroderma with bullous formation	>15.0[c]	Severe abdominal pain with or without ileus

Abbreviations: GI, gastrointestinal; GVHD, graft-vs-host disease.
SI conversion factor: To convert bilirubin to micromoles per liter, multiply by 17.104.
[a] Downgraded 1 stage if an additional cause of diarrhea has been documented.
[b] Used rule of nines to determine extent of rash.
[c] Downgraded 1 stage if an additional cause of elevated bilirubin has been documented.

Table 2. Overall Clinical Grading of Severity of Acute GVHD[9]

Grade	Degree of Organ Involvement
0	No stage 1-4 of any organ
1	Stage 1or 2 rash and no liver or gut involvement
2	Stage 3 rash, stage 1 liver involvement, or stage 1 gut involvement
3	Stage 0-3 skin rash with stage 2 or 3 liver involvement or stage 2-4 GI tract involvement
4	Stage 4 skin rash or stage 4 liver involvement

Abbreviations: GI, gastrointestinal; GVHD, graft-vs-host disease.

each organ site based on the extent of rash (skin), bilirubin level (liver), or volume of diarrhea (GI tract) (**Table 1**). Development of moderate (stage 2) or severe (stage 3 or 4) acute GVHD after HSCT is associated with a significant mortality rate.[4,9] The overall clinical grade of GVHD is determined by integrating the skin, liver, and GI tract stages (**Table 2**).

Acute GI GVHD most commonly involves the ileum, cecum, and ascending colon, but the stomach, duodenum, and rectum may also be affected.[1] Diarrhea, abdominal cramping, and GI bleeding are the hallmarks of intestinal involvement. Other clinical manifestations include nausea, vomiting, distention, and paralytic ileus.[1,2] Endoscopy is often used to evaluate and diagnose acute GI GVHD. Endoscopic findings of acute GI GVHD range from normal mucosa to extensive edema, mucosal sloughing, and diffuse bleeding.[1] Endoscopic biopsies are helpful in establishing the suspected diagnosis, and on histologic examination, crypt cell necrosis is observed with accumulation of degenerative material in the dead crypts.[4,10]

The concerning physical examination findings associated with acute GI GVHD frequently prompt surgical consultation. However, the role of surgical intervention in and the natural history of acute GI GVHD are poorly defined. The standard treatment of acute GVHD, irrespective of site, is corticosteroids.[1] The indications for surgical or percutaneous intervention are rarely reported and the benefits of surgery are unclear. Finally, the long-term consequences of GI GVHD in patients who survive the acute presentation remain largely unknown.[1,11-13]

We reviewed our experience with patients with severe acute GI GVHD after HSCT for hematologic malignancies. We specifically sought to determine the indications for intervention, the extent and benefit of intervention provided, and the outcomes to define guidelines for the consulting surgeon.

METHODS

All patients undergoing HSCT for hematologic malignancies at Brigham and Women's Hospital and the Dana-Farber Cancer Institute since August 1986 were followed up prospectively. After obtaining institutional review board approval, we reviewed the medical records of all patients who experienced severe (stage 3 or 4) acute GI GVHD after HSCT from February 1997 through March 2005 (we selected February 1997 as the earliest time point because by that date, the databases from our 2 institutions were merged, ensuring maximal accuracy of the information). Graft-vs-host disease was staged and graded according to consensus criteria (Tables 1 and 2). Data on age at HSCT, specific hematologic malignancy, source of hematopoietic stem cells, dates of HSCT and diagnosis of acute GI GVHD, dates of death and/or last known follow-up, interventions, autopsy findings, pathology of biopsied specimens, computed tomography (CT) results, and complications of GI GVHD were collected. Perforation, obstruction, ischemia, hemorrhage, and abscess were considered surgically correctable problems.

RESULTS

DEMOGRAPHIC DATA

Sixty-three of 2065 patients (3%) undergoing HSCT for hematologic malignancies from February 1997 to March 2005 were diagnosed clinically with severe (stage 3 or 4) acute GI GVHD. Demographic data, indications for HSCT, and details regarding HSCT for the 63 involved patients are shown in **Table 3**. The most common hematologic malignancies were acute myelogenous leukemia (15 patients; 24%), chronic myelogenous leukemia (11 patients; 18%), and myelodysplastic syndrome (11 patients; 18%). Hematopoietic stem cell transplantation was performed from matched unre-

lated donors in 38 of 63 patients (60%), matched related donors in 18 (29%), mismatched unrelated donors in 6 (10%), and other in 1 (2%). Hematopoietic stem cells were harvested from the peripheral blood of donors for 38 patients (60%) and the bone marrow for 25 patients (40%).

DIAGNOSIS AND MANAGEMENT OF GI GVHD

By definition, all patients with GI GVHD had diarrhea. The median time from HSCT to diagnosis of acute GI GVHD was 23 days (range, 6-99 days) (**Table 4**). The severity of GI GVHD based on volume of diarrhea (Table 1) was stage 3 in 18 patients (29%) and stage 4 in 45 patients (71%). Clinical diagnosis was confirmed histologically by endoscopic biopsy in 53 of 63 patients (84%). Generally, surgical consultations were obtained when patients exhibited increasing amounts of diarrhea, abdominal distention, and particularly abdominal pain, with or without persistent fever, positive blood cultures, or rectal bleeding.

Computed tomography findings were frequently equivocal. Of the 50 patients (79%) who underwent CT scans, 32 (64%) had bowel wall thickening, 10 (20%) had a normal-appearing bowel, and 8 (16%) had nonspecific findings. These findings were identified on the first CT scans performed after the diagnosis of acute GI GVHD.

CASE OF GI GVHD REQUIRING INTERVENTION

All patients diagnosed with acute GI GVHD were initially treated with immunosuppression. Only 1 patient ultimately underwent a surgical intervention. This patient was a 53-year-old woman diagnosed with stage 4 GI GVHD three weeks after HSCT for acute myelogenous leukemia. She was treated with corticosteroids and discharged to her home. Her symptoms improved and she remained stable for several weeks. However, she then developed progressively worsening diarrhea, abdominal distention, and abdominal pain. An abdominal CT scan revealed multiple dilated loops of small bowel with diffuse bowel wall thickening consistent with GI GVHD. No transition point was identified. Owing to progressive abdominal pain, the patient underwent an exploratory laparotomy. No ischemic bowel or sites of obstruction were identified. Adhesiolysis was performed, but no bowel was resected. The patient died 6 days later of sepsis and multisystem organ failure; no autopsy was performed.

OUTCOMES

To date, 52 of the 63 patients (83%) have died (**Table 5**). The median time to death after HSCT was 119 days (range, 41-482 days) and the median time to death from diagnosis of GI GVHD was 85 days (range, 11-458 days). Thirty-one of the 52 deceased patients (60%) underwent autopsy; none died of a surgically correctable cause.

Eleven of 63 patients (17%) were alive at the last follow-up a median of 1376 days (range, 214-2618 days) after HSCT (median, 1352 days after diagnosis of GI GVHD; range, 191-2599 days). One patient experienced diarrhea following laparoscopic cholecystectomy approximately 4 months after diagnosis of GI GVHD. This was presumed to represent a relapse of GI GVHD and resolved with treatment with steroids. No GI complications such as strictures, malabsorption, hemorrhage, or obstruction have yet been observed in this cohort.

Table 3. Demographic Data

Characteristics	No. (%) (N=63)
Sex	
Male	36 (57)
Female	27 (43)
Age at HSCT, y	
Mean	44.0
Median	47.6
Range	19.0-68.7
Hematologic malignancy	
Acute myelogenous leukemia	15 (23.8)
Chronic myelogenous leukemia	11 (17.5)
Myelodysplastic syndrome	11 (17.5)
Chronic lymphocytic leukemia/ prolymphocytic leukemia	8 (12.7)
Non-Hodgkin lymphoma	8 (12.7)
Hodgkin disease	3 (4.8)
Acute lymphoblastic leukemia	2 (3.2)
Multiple myeloma	2 (3.2)
Aplastic anemia	1 (1.6)
Other	2 (3.2)
Type of transplant	
Matched unrelated donor	38 (60.3)
Matched related donor	18 (28.6)
Mismatched unrelated donor	6 (9.5)
Other	1 (1.6)
Source	
Peripheral blood stem cells	38 (60.3)
Bone marrow	25 (39.7)

Abbreviation: HSCT, hematopoietic stem cell transplantation.

Table 4. Diagnosis and Extent of Acute GI GVHD

	No. (%)
Interval from HSCT to GI GVHD, d (n=63)	
Mean	33.3
Median	23.0
Range	6-99
Stage of GI GVHD (n=63)	
3	18 (28.6)
4	45 (71.4)
Confirmed by biopsy (n=63)	
Yes	53 (84.1)
No	10 (15.9)
Site of GI GVHD biopsy confirmation (n=53)	
Stomach	4 (7.5)
Small bowel	6 (11.3)
Colon and/or rectum	43 (81.1)

Abbreviations: GI GVHD, gastrointestinal graft-vs-host disease; HSCT, hematopoietic stem cell transplantation.

Table 5. Outcomes of Patients With Stage 3 or 4 GI GVHD

Outcome	Days, No.
Follow-up (n=11)[a]	
Mean	1438
Median	1376
Range	214-2618
Time to death from HSCT (n=52)	
Mean	151
Median	119
Range	41-482
Time to death from GI GVHD diagnosis (n=52)	
Mean	116
Median	85
Range	11-458

Abbreviations: GI GVHD, gastrointestinal graft-vs-host disease; HSCT, hematopoietic stem cell transplantation.
[a] Follow-up data for survivors.

Table 6. Dana-Farber/Brigham and Women's Cancer Center Guidelines for Surgical Consultation and Intervention for Severe Acute GI GVHD

Indications for surgical consultation[a]
Pneumoperitoneum
Pneumatosis intestinalis
Ischemic bowel
Bowel obstruction
Intraperitoneal hemorrhage
Intraluminal hemorrhage
Abdominal and/or pelvic abscess
Acute abdominal pain/tenderness
Relative indications for operative or percutaneous intervention[b]
Pneumoperitoneum
Pneumatosis intestinalis
Ischemic bowel
Bowel obstruction, refractory to conservative management
Intraperitoneal hemorrhage, with evidence of ongoing bleeding
Intraluminal hemorrhage, refractory to endoscopic intervention
Abdominal/pelvic abscess
Peritonitis or progressive abdominal pain/tenderness

Abbreviation: GI GVHD, gastrointestinal graft-vs-host disease.
[a] Isolated computed tomography findings of bowel wall thickening do not require surgical consultation in the absence of additional listed findings. However, such patients should be carefully monitored.
[b] Occasionally pneumoperitoneum and pneumatosis intestinalis may be managed conservatively in the absence of peritonitis or hemodynamic instability. Likewise, not all cases of ischemic colitis require surgical intervention. If colonoscopy shows evidence of colitis, in the absence of other findings necessitating intervention, observation may be appropriate at the discretion of the surgeon.

COMMENT

An increasing number of patients are undergoing allogeneic HSCT for hematologic malignancies. Consequently, surgeons will be asked to evaluate patients with one of its major complications, acute GI GVHD, more frequently. Given the generally ill health of this patient population and the relative rarity of this condition in general surgical practice, it is imperative that surgeons understand the natural history of and indications for intervention in this emerging dilemma.

The incidence of clinically severe (stage 3 or 4) GI GVHD in patients undergoing HSCT in this series was 3% (63 of 2065 patients). Others have reported incidences of intestinal GVHD ranging from 13%[12] to 50%.[5] However, those authors did not report the incidence based on stage, thereby making direct comparison to our series difficult.

Surgical consultation is generally recommended for patients with onset of profuse diarrhea (>500 mL/d), temperature higher than 38°C, abdominal pain, and GI hemorrhage after HSCT.[5] Because many patients are taking immunosuppressive agents after HSCT, symptoms of peritonitis may be masked; thus it is difficult to rely on abdominal examination. Theoretically, CT scans of the abdomen and pelvis could help identify potentially correctable surgical problems such as perforation, obstruction, ischemia, hemorrhage, and abscess. Of the 50 patients in this series who underwent CT scans, 32 (64%) had bowel wall thickening, a rather nonspecific finding that does not warrant immediate surgical intervention. Kalantari et al[14] reviewed the abdominal CT scans of patients with a confirmed diagnosis of GI GVHD and found that bowel wall thickening was evident in at least 1 site in all 22 cases examined. There was no predilection for any specific segment(s) of bowel. Clearly, better methods of identifying surgical emergencies are needed.

Typhlitis (or necrotizing enterocolitis) may clinically mimic GI GVHD in that it primarily occurs in immunosuppressed patients and presents with fever, abdominal pain, and potentially watery or bloody diarrhea.[15] However, in contrast to GI GVHD, typhlitis is usually localized to the cecum and/or ascending colon and terminal ileum, and patients usually report focal right lower quadrant pain. Computed tomography may be helpful in distinguishing typhlitis, as it will frequently show a fluid-filled, dilated, and distended cecum. Distinction between the two is imperative, as the treatment of typhlitis involves broad spectrum antibiotics, whereas first-line treatment of GVHD is corticosteroids.[15] This reflects a key difference between the 2 diseases; typhlitis has an infectious etiology, whereas GI GVHD has an immunologic one.

In this series of 63 patients with acute GI GVHD, only 1 patient required intervention. This patient underwent a nontherapeutic laparotomy. However, this has not been the case in other series. Chirletti et al[5] reviewed a series of 36 patients with acute GI GVHD after allogeneic bone marrow transplant. Seven had GI emergencies, with 3 requiring laparotomy for perforation (2 patients) or GI hemorrhage from a cecal ulceration (1 patient) and 1 requiring embolization for GI hemorrhage. The remaining patients, including 1 with focal peritonitis and 2 with hemorrhage, were managed nonoperatively. The authors advocated an aggressive surgical approach when medical treatment fails. Others have also reported cases of acute GI hemorrhage after the development of GI GVHD that have required laparotomy.[16-18] In each of these cases, the findings necessitating intervention were all focal.

Other investigators have argued that owing to the generally diffuse nature of this disease, surgical or other intervention is often not successful. Shabahang et al[19] noted that surgical resection of bowel segments with cytomegalovirus ulceration in the setting of GI GVHD had only

short-term success owing to diffuse disease. Likewise, Jones et al[11] reported that surgical resection for diffuse multifocal hemorrhage of the small intestine in patients with severe GI GVHD with concomitant thrombocytopenia was usually not successful and thus should not be attempted. The authors recommended aggressive resuscitation, correction of thrombocytopenia, and, if bleeding persisted, endoscopic intervention.[11] Angiographic intervention may also be considered.

The mortality rate of 83% for those with stage 3 or 4 GI GVHD reported in this series is high. Chirletti et al[5] reported a mortality rate of 30% to 60% in patients with acute grade 2 to 4 GI GVHD. However, neither that nor any other case series specifically detailed the mortality rate for those patients with severe (stage 3 or 4) GI GVHD. Therefore, it is difficult to directly compare the mortality rate from the present series to that of other series.

Although the mortality rate in patients with acute GI GVHD is high (median time from HSCT to death, 119 days), the 11 living patients in our series have survived a median of 1376 days after HSCT. Patients who survive the bout of acute GVHD and other immediate complications following HSCT may develop long-term complications. One particular problem noted with chronic cases of GI GVHD is the development of gastric or intestinal strictures, occasionally necessitating bowel resection or stricturoplasty.[11,16,20] While no such problems were observed in this series, all surviving patients are being followed up closely.

Based on our institutional experience and the available literature, we propose guidelines for obtaining surgical consultations and proceeding with operative or percutaneous interventions (**Table 6**). The limited data available suggest that surgeons should carefully evaluate these patients when concerning findings are present. The decision to operate should be approached judiciously, as few will truly benefit from laparotomy. No patients in the current series who underwent autopsy died of a surgically correctable cause. In other series, most patients who needed intervention generally required percutaneous drainage or limited bowel resection. Proximal diversions (stomas) alone were rarely beneficial.[5]

In conclusion, our large single-center experience with severe acute GI GVHD reviewed from a surgical perspective reveals that operative intervention is rarely therapeutic. However, as noted in other series, rare cases progress to perforation or hemorrhage that is unresponsive to medical management. Therefore, mature surgical judgment is necessary to confirm the absence of surgically reversible problems, thus avoiding unnecessary operations in this challenging patient population.

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