Gastric Bleeding Due to Graft-vs-Host Disease

Discrepancy Between Endoscopic and Histologic Assessment

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Abstract

Gastric bleeding due to graft-vs-host-disease (GVHD) is rare after allogeneic hematopoietic stem cell transplantation, and the interrelationship between endoscopic and histologic assessment has not been well studied. Four patients with documented gastric bleeding due to GVHD were evaluated retrospectively. The endoscopic findings varied markedly and included mild mucosal edema with focal erythema, diffuse erythema with mucosal oozing, and diffuse polypoid indurations with multiple bleeding ulcerations. The histologic features of endoscopic biopsy specimens also varied from scattered apoptotic epithelial cells in one end to denudation of the epithelium with crypt necrosis in the other. The endoscopic findings could not accurately predict the histologic grading of GVHD. Nevertheless, gastric bleeding resolved in 3 patients with increasing intensity of immunosuppression. There was significant disparity between the endoscopic and histologic assessment of the severity of GVHD, and careful adjustment of immunosuppressive therapy might be warranted.

Graft-vs-host disease (GVHD) is a significant cause of morbidity and mortality after allogeneic hematopoietic stem cell transplantation (HSCT), occurring in up to 75% of these patients, depending on the patient population. GVHD involving the upper gastrointestinal (GI) tract is common after allogeneic HSCT, with an estimated incidence of at least 22%, and is characterized by anorexia, nausea, vomiting, abdominal pain, and bleeding. Gross GI bleeding develops in 5% to 15% of HSCT recipients during the first 100 days, but many more have occult bleeding. In addition to GVHD, the causes of bleeding also might include mucosal trauma from retching, acid-peptic ulcers, and ulcers caused by infection. Bleeding in GVHD is from areas of mucosal defect of the involved bowel, most commonly the distal small bowel and the cecum. Gastric bleeding due to GVHD is rare, and the endoscopic and histologic features have not been well-studied. Furthermore, the diagnosis of GVHD of the stomach itself could be difficult, not only because of the nonspecific clinical symptoms and nonspecific findings of endoscopic evaluation, but also owing to many factors, particularly cytomegalovirus (CMV) infection, which can confound the histologic interpretation.

The goal of this study was to demonstrate the endoscopic and histologic features of gastric GVHD complicated by gastric bleeding. Four patients with gastric bleeding due to histologically proven gastric GVHD were included in the study. Concomitant CMV infection was excluded carefully. Gastric bleeding of varied degrees could be found directly by endoscopic examinations, and blood transfusions were given to all patients to treat the rapid drop in the hemoglobin concentration. We use these 4 cases to illustrate the great variability of endoscopic and histologic findings among patients with gastric bleeding due to
GVHD, particularly the disparity between endoscopic and histologic assessments of the severity of GVHD.

Materials and Methods

Patients

Of 48 consecutive adult patients who received allogeneic HSCT at China Medical University Hospital, Taichung, Taiwan, between November 1998 and December 2003, 4 had gastric bleeding due to histologically proven gastric GVHD and were included in the study. The details of allogeneic HSCT at our center were published previously. Characteristics of the 4 patients are listed in Table I. The date of the first day of stem cell infusion was considered day 0, the reference point for timing of all subsequent events. One patient (case 4) had primary graft failure and received a second transplant from a brother with a 1-locus mismatch 69 days after the first transplant. The first day of stem cell infusion of the second transplant was considered day 0 for this patient. The conditioning treatments before transplantation were myeloablative in cases 1 and 3 and for the first transplant in case 4. The conditioning treatments were nonmyeloablative in case 2 and for the second transplant in case 4. Chimerism studies determined by cytogenetics (cases 1 and 3) and short tandem repeats (cases 2 and 4) at various times after transplantation showed persistent donor chimerism.

Clinical Evaluation

All 4 patients had nausea, vomiting, anorexia, melena, and hematemesis. There also was a marked drop in the hemoglobin concentration, and transfusions of RBCs were given to all patients. At the onset of GI bleeding, all 4 patients had clinical evidence of GVHD involving the skin, liver, or bowel, and in 3 patients, the GVHD was documented histologically (Table 1). During the period of GI bleeding and before each endoscopic examination, platelet transfusions were given as needed to keep the platelet count at more than $80 \times 10^3/\mu L$ ($80 \times 10^9/L$). After the histologic documentation of gastric GVHD, prednisolone was added to the therapeutic regimen for patient 2, and the intensity of baseline immunosuppressive therapy was increased by increasing the dosage of prednisolone (patients 1 and 4) or by adding antithymocyte globulin and mycophenolate mofetil to the regimen (patient 3).

Endoscopic and Histologic Evaluation

Endoscopies were performed to investigate the cause of GI bleeding or to evaluate the treatment response. A total of 7 endoscopies were performed (3 for patient 1, 2 for patient 2, and 1 each for patients 3 and 4), and 31 biopsy specimens (24 from the stomach and 7 from the duodenum) were taken from the area of mucosal defect, as determined by the endoscopists on a case-by-case basis. Specimens obtained from endoscopic biopsies were fixed in buffered formalin and embedded in paraffin, from which serial 5-µm-thick sections were cut. Sections of each specimen were stained with H&E for routine histopathologic examination and with methenamine silver for the detection of fungi.

CMV Detection

Because of the high risk of having CMV disease, all patients underwent surveillance viral cultures of blood, urine, stool, and throat every 7 days after myeloid engraftment and during immunosuppressive therapy. Immunohistochemical

Table I
Demographic and Clinical Characteristics of Patients

<table>
<thead>
<tr>
<th>Case No./ Sex/Age(y)</th>
<th>Disease</th>
<th>Conditioning Regimen</th>
<th>Donor</th>
<th>GVHD Prophylaxis</th>
<th>Transplant</th>
<th>Onset of GI Bleeding</th>
<th>Date of Endoscopy</th>
<th>GVHD Other Than Stomach</th>
<th>Negativ e CMV Studies a</th>
<th>Response to Treatment/ Final Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/45</td>
<td>AML, second relapse</td>
<td>TBI/Cy</td>
<td>MSD, G2P2, F</td>
<td>CSA/MTX</td>
<td>PB SCT</td>
<td>D135</td>
<td>D141, D148, D204</td>
<td>Skin (H); liver (C)</td>
<td>Culture, IA</td>
<td>Bleeding resolved/ alive, 22+ mo</td>
</tr>
<tr>
<td>2/M/23</td>
<td>HD, second CR</td>
<td>Flud/Bu</td>
<td>MUD, M</td>
<td>CSA/MTX/ ATG</td>
<td>BMT</td>
<td>D47</td>
<td>D50, D75</td>
<td>Skin (C)</td>
<td>Culture, IA</td>
<td>Transient response/ died, D83</td>
</tr>
<tr>
<td>3/M/31</td>
<td>AML, first CR</td>
<td>Bu/Cy</td>
<td>MSD, G2P2, F</td>
<td>CSA/MTX</td>
<td>PB SCT</td>
<td>D159</td>
<td>D168</td>
<td>Liver and colon (H)</td>
<td>Culture, IA, PCR</td>
<td>Bleeding resolved/ died, D200</td>
</tr>
<tr>
<td>4/M/38 t</td>
<td>CML, chronic phase</td>
<td>Bu/Cy; Flud/ Melphalan</td>
<td>MUD, M</td>
<td>1-antigen mismatched brother</td>
<td>CSA/MTX/ ATG</td>
<td>BMT followed by PB SCT</td>
<td>D111</td>
<td>D114</td>
<td>Liver (H); skin (C)</td>
<td>Culture, IA, PCR</td>
</tr>
</tbody>
</table>

AML, acute myelogenous leukemia; ATG, antithymocyte globulin; BMT, bone marrow transplantation; Bu, busulfan; C, clinically documented; CML, chronic myelogenous leukemia; CMV, cytomegalovirus; CR, complete remission; CSA, cyclosporine-A; Cy, cyclophosphamide; D, day (the first day of stem cell infusion was considered day 0); Flud, fludarabine; G, gravida; GI, gastrointestinal; GVHD, graft-vs-host disease; H, histologically documented; HD, Hodgkin disease; IA, immunohistochemical analysis; MSD, HL-A-matched sibling donor; MTX, methotrexate; MUD, HL-A-matched unrelated donor; P, para; PB SCT, peripheral blood stem cell transplantation; PCR, polymerase chain reaction; TBI, total body irradiation.

a Surveillance culture.

t Increased dosage of prednisolone in cases 1 and 4; added prednisolone in case 2; added ATG/mycophenolate mofetil in case 3.

t First transplant, received busulfan/cyclophosphamide; second transplant, fludarabine/melphalan. The first day of stem cell infusion of the second transplant was defined as day 0 for this patient.
study using a monoclonal antibody (Novocastra Laboratories, Newcastle upon Tyne, England) against the latent antigen of CMV was performed on each specimen from endoscopic biopsies to detect CMV infection. For more sensitive detection of CMV reactivation, polymerase chain reaction also was used with the method and primer sequences described previously to detect CMV viremia in cases 2, 3, and 4.

Results

The first endoscopy in case 1 on day 141 showed diffuse polypoid indurations with mucosal oozing in the body and antrum, and a submucosal tumor (extramedullary leukemia) of the stomach was suspected. Nevertheless, histologic examination of gastric biopsy specimens showed nonspecific gastritis without evidence of leukemic cell infiltration or GVHD. Because nausea, vomiting, and intermittent hematemesis persisted despite empiric treatment with omeprazole, endoscopy and biopsy were repeated 1 week later, on day 148. The endoscopic features of Image 1A were more severe than those found previously, and a submucosal tumor (extramedullary leukemia) still was suspected. Nevertheless, histologic examination of the gastric biopsy specimens showed marked crypt necrosis with numerous apoptotic epithelial cells of Image 1B. After increasing the dosage of prednisolone, the GI symptoms and bleeding resolved gradually. Endoscopy repeated on day 204 showed marked improvement, and only mild mucosal edema with focal erythema was found of Image 1C.

The endoscopic features in case 2 showed nonspecific mild mucosal edema with focal erythema and a few hemorrhagic spots of Image 2A. Histologic examination of endoscopic biopsy specimens showed scattered apoptotic epithelial cells at the neck region between the crypts and the glands of Image 2B.

Anatomic Pathology / ORIGINAL ARTICLE

A

B

C

Image 1A (Case 1) Endoscopic and histologic features. A, Endoscopy performed on day 148 showed diffuse polypoid indurations with multiple bleeding ulcers in the body and antrum. B, Endoscopic biopsy of stomach on day 148 showed crypt necrosis (arrowhead) and epithelial denudation (arrows) (H&E, ×100). Higher magnification (insets, ×600) showed some apoptotic epithelial cells characterized by the presence of karyorrhectic debris. C, Endoscopy performed on day 204, 2 months after treatment with an increased dosage of prednisolone, showed marked improvement in the gastric condition.
The endoscopic features in case 3 showed that the stomach was involved more severely, and diffuse erythema with active mucosal oozing was found Image 2C. However, findings of histologic examination of the endoscopic biopsy specimen were similar to those in case 2, and only a few scattered apoptotic epithelial cells were found Image 2D.

The endoscopic features in case 4 were similar to those in case 2, showing only mild mucosal edema and focal erythema Image 2E; nevertheless, the abnormalities shown by the endoscopic biopsy were much more prominent than predicted, and crypt destruction with numerous apoptotic cells was found Image 2F.

Clinically, patients 1 and 3 had more severe bleeding and needed more transfusions and prolonged blood transfusion support, which correlated well with the endoscopic findings (Image 1A and 2C).

Response to the increased dosage of corticosteroid was good in patients 1, 3, and 4, and GI bleeding resolved gradually. However, GVHD of the liver progressed in patient 3, and he died of infection and multiple organ failure on day 200. The response to corticosteroid therapy was only transient in patient 2, and GI bleeding recurred. Endoscopy and biopsies were repeated on day 79, and the findings were similar to those on day 50. This patient died of infection and multiple organ failure on day 83.

The findings of endoscopy and endoscopic biopsies of the duodenum were similar, but less severe involvement was found in cases 1 and 3 and apparently normal findings were found in cases 2 and 4.
CMV was not detected in any patient by using methods of surveillance culture, immunohistochemical study on gastric biopsy specimens, and polymerase chain reaction on blood specimens at the time when GI bleeding due to GVHD was diagnosed.

Discussion

The most prominent symptoms of GVHD involving the upper GI tract are anorexia, nausea, vomiting, and, occasionally, abdominal pain. GI bleeding is not a common manifestation of GVHD and was present in only 6% of patients with upper GI biopsies positive for GVHD. In this report, we reviewed the clinical, endoscopic, and histologic features of gastric GVHD complicated by bleeding. Our data clearly demonstrate that the endoscopic findings varied markedly among these patients. The endoscopic features (diffuse polypoid indurations mimicking submucosal gastric tumor; Image 1A) in case 1 have not been reported previously in patients with gastric GVHD, and extramedullary leukemia was our initial impression. A second endoscopic biopsy provided histologic documentation of gastric GVHD, but these polypoid lesions resolved completely after the dosage of prednisolone was increased (Image 1C).

The histopathologic features of the endoscopic biopsy specimens varied markedly among the 4 cases. According to the published histologic grading system for GI-GVHD (grade 1, increased crypt apoptosis; grade 2, apoptosis with crypt abscess; grade 3, individual crypt necrosis; grade 4, denudation of areas of mucosa), the most severe of the 4 cases was in patient 1 (grade 4), and the next was in patient 4 (grade 2). The histologic features in cases 2 and 3 could be classified only as grade 1. However, the severity of bleeding and the endoscopic findings showed the stomach was more severely involved in case 3 than in case 4. This indicates significant disparity could be found between endoscopic and histologic assessments of the severity of gastric GVHD with gastric bleeding.

Whether endoscopic findings can predict the histologic grade of GI-GVHD is still a subject of considerable debate. Frequent disparity between endoscopic and histologic assessments of the severity of GI-GVHD was noted in a study by Ponec et al. Nevertheless, a positive association between endoscopic grading and histologic grading of GI-GVHD was observed by Cruz-Correa et al. It is not known why different results were observed in the same patient population, although a different study design and a different endoscopic grading system could be important factors.

In the present study, we found that sampling error might be a more critical factor in this discrepancy. First, the grossly visible mucosal defect can be uneven in distribution, sometimes appearing as severe involvement in one area but appearing unremarkable at another site. At the second endoscopic examination in case 1, the gastric body and antrum were involved severely Image 3A, whereas the cardiac area was relatively normal Image 3B. Second, sampling error due to biopsy technique might occur, and different histologic grades could be found even in the same biopsy specimen. Image 3C illustrates different histologic grading within 1 specimen from case 1 obtained during the second endoscopic examination. The epithelium was relatively normal in the left lower quadrant, whereas mucosal denudation (arrow) with individual crypt necrosis (arrowhead) was found in the right upper quadrant.
quadrant. Such sampling error (eg, biopsy around the area of the left lower quadrant of Image 3C) might lead to an underestimation of the severity of GVHD. Therefore, it is of great importance to perform more biopsies for a more precise assessment of the severity of GVHD.

With increasing intensity of immunosuppression, gastric bleeding resolved gradually in 3 patients (1, 3, and 4) and improved transiently in patient 2. Despite the initial favorable response to immunosuppressive therapy, patients 2 and 3 eventually died of progressive GVHD and its complications. In fact, before gastric bleeding due to GVHD was diagnosed, all 4 patients had clinical and/or histologic evidence of GVHD involving other organs. This suggests that gastric bleeding due to GVHD might represent a more severe form of GVHD possibly associated with a dismal outcome. This presumption is consistent with the observation by Nevo et al, who demonstrated that bleeding complications correlated with GVHD severity and clearly identified a poor-outcome subgroup of patients with GVHD. Of course, more patients are needed to confirm the prognostic significance of gastric GVHD complicated by gastric bleeding. In addition, 1 question was unanswered by this study. The GVHD of patients we examined might be more severe than in patients with only anorexia or nausea, which were much more common in patients with gastric GVHD. The endoscopic and histologic findings in patients with less severe gastric GVHD might not be the same, and the correlation between endoscopic and histologic findings requires further investigation.

Gastric bleeding might be one of the manifestations of gastric GVHD. The endoscopic and histologic findings are highly variable in these patients, and significant disparity between endoscopic and histologic assessments of the severity of GVHD was observed. Careful adjustment of the
intensity of immunosuppressive therapy might be warranted not only for the treatment of gastric bleeding but also for the effective management of underlying GVHD.

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