Gastrointestinal Bleeding, the First Presentation of Acute GVHD in Two Patients with Thalassemia after BMT

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Engraftment by donor lymphocytes in an immunologically compromised host can result in donor T–cell activation against host major histocompatibility complex antigens, with resultant GVHD.

The acute form of GVHD (aGVHD) is characterized by erythroderma, cholestatic hepatitis, and enteritis. The intestinal symptoms of aGVHD include crampy abdominal pain and watery diarrhea, often with blood. The conditioning regimen and infectious agents may produce similar symptoms. Severe intestinal aGVHD is a life-threatening event and associated with high mortality.

In this case report, we describe two patients with major thalassemia who experienced acute gastrointestinal GVHD. One of them experienced it after peripheral blood transplantation at day +13, and the other after bone marrow transplantation at day +14. The first presentation was severe GI bleeding, and then 2 litters per day diarrhea. Besides standard prophylaxis with Cyclosporine and Methotrexate, Methylprednisolone 2mg/kg per day commenced because GI bleeding started and afterward supportive treatment means were continued. Following administration of Methylprednisolone, the amount of GI bleeding and diarrhea declined; in addition, the need for whole blood transfusion and blood products decreased. Both children had no problem in follow-up.

Engraftment evaluation by the VNTR method showed 100 percent validity. GI bleeding after transplantation can be a major presentation of aGVHD, which requires precise attention, and on-time treatment. The elimination of other causes of GI bleeding and diarrhea, in addition to the two other factors mentioned above, would increase the survival rate of patients greatly.

Key words: aGVHD, Gastrointestinal bleeding

Introduction:

Engraftment by donor lymphocyte in an immunologically compromised host (congenital, radiation or chemotherapy induced immune deficiency) could result in donor T cell activation against host major histocompatibility complex (MHC) antigens, with resultant GVHD.

GVHD is classified as acute, when occurring within the first 100 days after bone marrow transplantation, or chronic, when occurring after the first 100 days. The acute form of GVHD (aGVHD) is characterized with erythroderma, cholestatic hepatitis, and enteritis. Typically, aGVHD presentation starts around the 19th day (median), when patients are undergoing engraftation. It usually starts with a pruritic macular/popular rash on the ears, palms and soles, and may progress to involve the trunk and extremities, potentially becoming a more confluent erythroderma with bulla formation and exfoliation. Fever may or may not be present. Differential diagnosis considerations include immunosuppressive regimen toxicity, drug rash and viral or other infectious exanthems. Hepatic manifestations include cholestatic jaundice with elevated values of liver function tests. The differential diagnoses include hepatitis, veno-occlusive disease, or drug side effects. The intestinal symptoms of aGVHD include crampy abdominal pain and watery diarrhea, which is often bloody. The conditioning regimen and infectious agent might produce similar symptoms. Eosinophilia, lymphocytosis, protein-losing enteropathy, bone marrow aplasia (neutropenia, thrombocytopenia anemia), peripheral edema, and secondary infections may ensue. Factors related to the development of aGVHD include histocompatibility difference between donor and patient, gender mismatching, donor parity, age-active or relapsed malignancy at the time of transplantation, and increasing doses of radiation. Prevention and treatment of GVHD require various immunosuppressive agents.

CASE No 1:
Specifications and Clinical features

A 4 years old girl, the second child of the family, with A^+ blood group who had been suffering from major thalassemia and had been treated with whole blood transfusions since she was one years old. The donor was her 7-year-old brother, the first child of the family, with O^+ blood group, who was suffering minor thalassaemia. The girl had been experiencing infusion pump Desferal injection since she was 2.5 years old. She weighed 12 kg, which was 3SD less than standard for her age. No metabolic disorders or heart disease were detected. There was a A palpable spleen 3 cm under her rib edge; but no hepatomegaly was detected. A tenfold higher than standard liver iron concentration was reported. Liver biopsies revealed severe hemosiderosis without fibrosis. Ferritin's concentration was 504 mg/dl before transplantation. The patient with class II thalassaemia underwent allogeneic transplantation.

Peripheral blood transplantation
For allogeneic transplantation, her 7 year old brother was HLA matched found to be HLA identical, and the

method of transplant was PBSC. The preparation regimen (conditioning regimen) was Busulfan 3.5mg/kg/day and Cyclophosphamide 50mg/kg/day, both of which were administered for 4 days. The amount of injected cells was 7.2×10^8/kg MNC and 8×10^8/kg WBC. The aGVHD prophylaxis regimen consisted of Cyclosporine A and Methotrexate. Following transplantation, she showed skin GVHD presentation at day +11 in the form of erythema and pruritus of palms and soles (stage 1), and at day +13, she experienced a severe GI bleeding with rectorraghia and hematochezia; moreover, because of high volume loss she experienced hypotension and CVP (central venous pressure) drop, so she was hydrated and transfused with blood products (plasma, cryoprecipitate and platelet). After day +14, she presented bloody diarrhea in tremendous volumes, about 2 to 2.5 litters per day. She was managed by CVP line and underwent TPN (total parentral nutrition) and hydration. To reduce the volume of diarrhea and hematochezia, Octerotide 10μg/kg/day was administered but no improvement was noticed. According to the patient's condition, Methylprednisolone 2mg/kg/day was started which had an excellent outcome and reduced the diarrhea and bleeding. No pathogens were detected in stool and blood cultures; also CMV-PP65 antigen was negative. Furthermore, there was no evidence of a hemolytic process or fragmentation in peripheral blood smears. There was a rise in BUN and Cr, which corresponded with pre-renal azotemia, and was treated with hydration. There were no abnormal findings in sonography imagings. Endoscopic investigations depicted bleeding without apparent ulcers in her esophagus, stomach, and duodenum; except for microhematoma regions in the mucus layer of those areas. Colonoscopy also showed the same appearance as the upper GI tract. It was impossible to take biopsies from this organ because of the patient's condition. After the gradual regression of diarrhea, TPN was replaced by a regular diet because of the patient's tolerance. Follow up with the VNTR method at day +38 revealed a 100 percent validity of the donor's cells. In the mean time, repeated follow-ups showed the excellent health condition of the patient. The last follow up was on day +196.

CASE NO 2: Specifications and Clinical features:

A 6 year old girl patient, third child of the family, with B⁻ blood group, who had been suffering from major thalassemia and treated with whole blood transfusions since she was two years old. The donor was her ten year old sister, the first child of the family with A⁻ blood group. The girl had experiencing Desferal pump infusion since she was 4 years old. Noticeable findings on physical examination included slight maxillary bone deformity, splenomegaly palpable 3 cm under rib edge and no hepatomegaly. No metabolic disorders or heart disease were detected. Liver iron concentration had increased fivefold. Liver biopsies revealed a slight

deposition of iron without sever haemosiderosis or fibrosis. Ferritin concentration was 7.5 ng/ml before transplantation. The patient, with class I thalassaemia, underwent allogeneic transplantation.

Bone Marrow Transplantation

Her 10-year–old sister was the closest donor for allogeneic transplantation, considering the HLA compatibility and bone marrow gathering was done in the operating room. Preparation regimen (conditioning regimen) was Busulfan 3.5 mg/kg/day and Cyclophosphamide 50 mg/kg/day, both for 4 days. The amount of injected cells was $1/5 \times 10^8$/kg for MNC and 2.04×10^8/kg for WBC. Cyclosporine A and Methotrexate were implemented for aGVHD prophilaxis. Four days following transplantation, she presented a fever, so Piperaciline and Vancomycine were started after blood culture sampling. At day +14, she experienced rectorrhaghia and diarrhea. The volume of diarrhea was about 500 to 1000^{cc} per day, so, with a diagnosis of GVHD, Methylprednisolone 2mg/kg/day was commenced. Blood and stool cultures reported negative for pathogens. The CMV-PP65 antigen was negative too. The response to Methylprednisolone was favorable, the diarrhea was relieved and the bleeding stopped. Follow up with the VNTR method on day +38 revealed 100 percent validity of donor's cells. In the mean time repeated follow-ups showed the excellent health condition of the patient. The last follow-up on day +270.

Discussion

In thalassemic patients, if an HLA-identical family member is available, BMT should be performed before the patient develops advanced disease. Three risk factors that influence the outcome of BMT for thalassemia include hepatomegaly, portal fibrosis, and a history of inconsistent iron chelation before transplant. Other factors, such as the number of transfusions, ferritin level, degree of hemosiderosis, hepatic iron concentration and splenomegaly have no affect. Disease-free survival rates of up to 90% are obtained in children receiving BMT before the development of hepatomegaly or portal fibrosis. Hepatic hemosiderosis and portal fibrosis may improve after BMT if the damage is not extensive.

Virtually all patients develop a disturbance of the gastrointestinal tract following hematopoietic stem cell transplantation. The main problems experienced by patients can be grouped as follows:

- Graft–versus–host disease
- Opportunistic infection
- Toxicity due to drug, radiation, or total parenteral nutrition (TPN).

These are not exclusive and some or all may be present concurrently. Most patients experience oral mucositis, nausea, or vomiting and some degree of diarrhea especially during the first month posttransplant. The underlying causes require early diagnosis, as specific

antimicrobial/antiviral treatment or increased immune suppression may be required. There is an overlap between risk of infection, GVHD, and immune suppression. Severe intestinal or hepatic damage can result in significant morbidity and mortality, even when the donor stem cells have engrafted and are functioning.

GI symptoms prior to transplantation should be investigated, as the early posttransplant opportunity may be restricted by thrombocytopenia and neutropenia. A history of peptic ulcer disease or recent dyspepsia requires exclusion of active ulceration. Prior GI or biliary sepsis needs careful evaluation.

Causes of diarrhea after marrow transplantation are as follows:

- Chemotherapy or chemoradiotherapy
- Intestinal GVHD
- Intestinal infections–viral (CMV), parasite (Giardia, Strongyloides), fungal (Candida)
- Drugs (nonabsorbable antibiotics)
- Pseudomembranous colitis, secondary to antibiotic therapy and caused by Clostridium difficile

Clinical staging and grading of graft versus host disease

Stage	Skin	Liver	Intestinal Tract
+	Maculopapular rash <25% of body surface	Bilirubin 2-3 mg/100ml	>500 ml diarrhea/daily
++	Maculopapular rash 25%-50% of body surface	Bilirubin 3-6 mg/100ml	>1000 ml diarrhea/daily
+++	Generalized erythroderma	Bilirubin 6-15 mg/100ml	>1500 ml diarrhea/daily
++++	Generalized erythroderma with bullous formation and desquamation	Bilirubin > 15 mg/100ml	Severe abdominal pain with or without ileus

GVHD Grade	Skin Stage	Liver Stage	Intestinal Tract Stage	Decrease in Clinical Performance
I	+ to ++	0	0	None
II	+ to +++	+	+	Mild
III	++ to +++	++ to ++++	++ to +++	Marked
IV	++ to ++++	++ to ++++	++ to ++++	Extreme

Diarrhea usually develops after day 4 posttransplant and may be associated with abdominal pain. Stool cultures should always be taken. Mild symptoms are usually conventional antidiarrheal and antispasmodic medication (e.g., Codein phosphate 25-50 mg i.v. every 4 to 6 hours). A profuse watery or hemorrhagic diarrhea is most likely due to aGVHD or infective enteritis and can be a significant management problem. In a prospective study, 150 acute diarrheal episodes developed in 126 patients posttransplant were responsible for 48%, and an infection for 13% of these episodes. Intestinal infection was found in 20 of the 150 episodes and the agent involved included viruses (Astrovirus, Adenovirus, CMV, and Rotavirus) in 12 patients, nosocomially acquired bacteria (Clostridium difficile and Aeromonas) in 7 patients, and mixed infection in one patient. The clinical signs and symptoms in GVHD were similar. In 39% of episodes no clear etiology could be found for self-limited diarrhea. Abdominal pain and colic could be severe and distressing. Large volume secretory diarrhea (liters per day) is difficult to control, but usually settles with specific therapy of the underlying cause and adequate fluid replacement. Octreotide, up to doses of 400 µg TID, can substantially reduce stool output in both acute gut GVHD and chemoradiation–related toxicity. It is essential to perform endoscopy, in conjunction with stool culture, if a cause other than chemoradiotherapy toxicity is considered possible. Multiple biopsies should be taken as long as the platelet count is greater than 50×10^9/l and coagulation parameters are normal at the time of biopsy. Biopsy tissue should be rapidly processed and the tissue sections available for interpretation within 6 hours. Diarrhea of any cause markedly interferes with absorption of oral cyclosporine and can be an indication for institution, or continuation, of the intravenous preparation.

Other causes of gastrointestinal complication are bleeding. Minor GI bleeding is not infrequent in the early posttransplant period. It settles with correction of thrombocytopenia and abnormal clotting factor profiles. Causes include esophagitis (viral, fungal, or peptic), aGVHD, viral enteritis and perianal fissures or hemorrhoids.

Rarely the patient may experience high volume bleedingbut the more likely causes include:

- Duodenal or gastric ulcer
- Small bowel or colonic ulcer (often CMV)
- Previous rectal biopsy site
- Acute GVHD
- Gastric erosion

Appropriate endoscopic investigation is essential if bleeding is significant. Kaur and colleagues investigated overt GI bleeding in a series of 579 consecutive bone marrow transplant recipients. Bleeding manifestations included hematemesis (n= 24), melena (n= 8), hematochezia (n= 7), and combinations (n= 4). The median time from bone marrow infusion to the onset of overt GI bleeding was 7.5 (range 0 to 45) days. Fourteen patients had evidence of orthostatic hypotension attributable to GI bleeding. Upper endoscopy was performed in 26 patients: 18 had diffuse esophagitis and gastritis. Two patients with bleeding ulcers underwent electrocautery. Colonoscopy was performed in five patients and revealed a cecal ulcer on one subject, tumor recurrence in one patient, and colitis in another. No patient underwent surgical intervention. One patient died as a result of GI

bleeding. Persistent upper GI bleeding was treated with somatostatin, if platelet transfusion support was not effective. Grothaus and colleagues reported their experience with factor XIII replacement in patients with severe aGVHD of the bowel after allogeneic hematopoietic stem cell transplantation. After 8 days of factor XIII replacement and unchanged high-dose immunosuppression, they observed a significant reduction in the red blood cell requirement for 21 of 28 patients.

In our first patient, severe bleeding and diarrhea were relieved by supportive management including balance of fluid and electrolities, blood and products, and high doses of immunosuppresion in association with methylprednisolone 2mg/kg/day. Subscription of methylprednisolone at the proper time could be life saving in patients with aGVHD. Initial manifestations in the second patient who did not have any skin symptoms were gastrointestinal GVHD with hemorrhage and diarrhea. Subsequent to BMT, when there are atypical intestinal or other organ symptoms, it is important to keep in mind that a `GVHD may be present with different manifestations.

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