Published in final edited form as:

Transplant Proc. 2014 June ; 46(5): 1536–1539. doi:10.1016/j.transproceed.2013.12.066.

Intestinal Ischemia following Allogeneic Stem Cell Transplantation: A report of four cases

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Abstract

Gastrointestinal ischemia following allogeneic bone marrow transplantation is a rare complication not well-described in the literature. Herein, we retrospectively review charts of four patients that developed intestinal ischemia following allogeneic bone marrow transplantation at our institution. The patients were found to be predominately younger males that presented with nonspecific abdominal pain. Graft versus host Disease was a common finding among all patients. Laboratory values suggestive of microangiopathy were present in two patients. Obesity and hypertriglyceridemia were of the cardiovascular risk factors that were found in patients. The development of intestinal thrombotic microangiopathy and cardiovascular risk factors after allogeneic bone marrow transplant may predispose patients to gastrointestinal ischemia and may portend a poor prognosis.

Introduction

Gastrointestinal complications following allogeneic bone marrow transplantation are common and include Graft versus host Disease (GVHD), opportunistic infections, and medication toxicity [1]. Intestinal ischemia after allogeneic stem cell transplant is a phenomenon that has not been previously well-described in the literature; however there are few reports of gastrointestinal perforation following allogeneic bone marrow transplantation [2–4]. Of these referenced the intestinal complications were notably reported in association with GVHD [3, 4] and thrombotic microangiopathy (TMA) [2, 3, 5].

336 patients received allogeneic bone marrow transplantation at the University of Kansas Medical Center from August 2008 until December 2012 and four of these developed intestinal ischemia within 36 months post-transplant. In this retrospective study, these four

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patients were studied to characterize their clinical presentation, possible risk factors for developing ischemia including cardiovascular risk factors, CMV status, and steroid use, the association with Graft versus host Disease and TMA, and their prognoses.

Methods

A retrospective chart review was performed on four patients that developed gastrointestinal ischemia following allogeneic bone marrow transplantation from August 2008 until December 2012. One of these patients was briefly reported previously [3]. Independent chart and pathology reports were reviewed to determine risk factors for developing intestinal ischemia. Patient characteristics including gender, age, underlying disease, days post transplantation, and symptom presentations were evaluated. Labs suggestive of TMA including complete blood count, peripheral smear, haptoglobin, and lactate dehydrogenase were collected. Risk factors including CMV status and steroids use at the time of presentation were reviewed. Cardiovascular risk factors including history of dyslipidemia, diabetes, hypertension, tobacco use, family history of coronary artery disease, obesity, and prior CVAs were all studied. Association with Graft versus host Disease at the time of intestinal ischemia was evaluated. Finally, surgical pathology findings and outcomes from each case were reviewed.

Results

Patient Characteristics

The four patients with gastrointestinal ischemia following stem cell transplantation consisted of three males and one female with ages 21 to 57 years old. Patient background characteristics are listed in table 1. Their diagnoses consisted of acute myelogenous leukemia, myelodysplastic Syndrome, Hodgkin's lymphoma, and myelofibrosis. Three of the four patients (#1, 3, 4) had nonspecific abdominal pain on presentation.

Clinical Laboratory Findings and potential Risk Factors

Clinical laboratory values were reviewed for each patient to determine which risk factors and confounders were associated with the development of gastrointestinal ischemia following allogeneic bone marrow transplantation. Lipid panels obtained within 18 months of presentation were reviewed for each patient. LDL was elevated to 175 mg/dl in one patient (#1), however only two of the patients had a documented low density lipoprotein level. Two of the four patients (#2, 3) did have had hypertriglyceridemia. One patient (#1) had a past medical history of hypertension. None of the patients had a history of diabetes mellitus, tobacco use, or family history of coronary artery disease. Obesity is associated with cardiovascular disease through these established risk factors so body mass index was reviewed. Two of the patients (#2, 3) had obesity with BMI > 30. One patient had morbid obesity with BMI > 35 (#1). None of the patients had prior history of cerebrovascular events. Cardiovascular risk factors and influences are listed in table 2. General risk factors reviewed included steroid use and CMV status. All of the patients were CMV negative. Three of the four patients (#1, 2, 4) were on steroids at the time of presentation.

The association with microangiopathy was also reviewed in each patient. All patients had an elevated lactate dehydrogenase; however two of the patients (#2, 3) had significant elevations greater than 500. Patient #2 also had a low haptoglobin of 14 and patient #3 had a haptoglobin of 8. Three of the patients (#2, 3, 4) had thrombocytopenia. Three of the four patients (#1, 2, 3) had elevated serum creatinine levels above baseline. Peripheral smear was performed on two of the four patients (#2, 3) to evaluate for microangiopathic hemolytic anemia. Patient number #2 and #3 had schistocytes.

All of the patients had the diagnosis of GVHD during the development of intestinal ischemia. Patient #1 had skin and liver involvement. Patient #2 had chronic GVHD of the gastrointestinal tract. Patient #3 had skin and gastrointestinal involvement. Patient #4 had skin, liver, and gastrointestinal involvement.

Pathology Findings

All of the patients proceeded with surgical intervention. Patient #1 had a partial right colectomy and pathology revealed marked ischemic necrosis of the right colon. Patient #2 had a subtotal colectomy and ileostomy placed. Pathology revealed ischemic necrosis. Patient #3 underwent a hemicolectomy and pathology revealed chronic ischemic changes, intestinal fibrosis, and focal ulceration of the right colon and small intestines. Patient #4 had a sigmoidectomy and descending colostomy with Hartman's pouch. Pathology revealed mucosal necrosis with focal transmural necrosis and acute transmural inflammation. Patient #2 was previously reported to have evidence of thrombosis of intestinal vessels [3].

Outcomes

Patient #1 and #4 recovered following surgical intervention, while patient #2 and #3 died following surgery. Patient #2 died of respiratory and liver failure and patient #3 died of septic shock.

Discussion

Reports regarding intestinal ischemia in allogeneic bone marrow transplant patients are scarce in the literature. One report describes a patient presenting with diarrhea one hundred days post-transplant and radiologic investigation revealed bowel perforation and thrombotic microangiopathy [2]. Another case in the literature reported colonic perforation in a surgical patient in the setting of GVHD[4] following bone marrow transplantation. In a study of 251 patients post allogeneic bone marrow transplantation, 16 patients that presented with abdominal pain, diarrhea, and intestinal bleeding were found to have histopathologic evidence of intestinal thrombotic microangiopathy (i-TMA). Pathology showed thrombonecrosis suggesting evidence of ischemic colitis secondary to the microangiopathy [5]. A post-transplant patient with chronic GVHD and i-TMA also developed pneumoperitoneum and was described in a case report to have intestinal ischemia on surgical pathology [3]. Evidence suggests that intestinal thrombotic microangiopathy and GVHD can lead to bowel ischemia; however its association has only been documented in the cases cited above.

Here we present four cases of post-transplant intestinal ischemia confirmed by surgical pathology. All of the patients were relatively young with ages ranging from 21 to 57. Prior studies in the literature describing post-transplant complications of perforation and i-TMA had similar ages ranging from 20 to 53 [2, 3, 5]. Three of our four patients were male suggesting possible gender predominance. In the study cited above reporting 16 patients with i-TMA, 13 out of the 16 patients were male [5]. Nonspecific abdominal pain was the most common clinical presentation in three of our four patients. The 16 patients from the i-TMA study presented with lower abdominal pain, diarrhea, and intestinal bleeding [5]. The case reported by Hewamana et al. presented with diarrhea and rash and the patient was found to have intestinal perforation and i-TMA. [2]

A well-known complication following allogeneic stem cell transplantation is GVHD. One case report describes colonic ischemia and perforation in the setting of GVHD [4]. Out of the sixteen patients found to have ischemia in the i-TMA study, fourteen of them had the diagnosis of acute GVHD. Patients surviving greater than 100 days post-transplant were considered to have chronic GVHD and six of the fourteen did fall into this population [5]. A common finding amongst all of our patients was a diagnosis of chronic Graft versus host Disease and all presented greater than 100 days post transplantation.

Two of our patients had evidence of TMA with schistocytes present on peripheral smear, low haptoglobin, and elevated LDH. Three of our four patients had acute renal failure and two of these were also the patients with evidence of TMA. The other cases cited in the literature reporting TMA used the same criteria for diagnosis [5]. A common finding between our patients and the ones in the literature presenting with TMA was an underlying diagnosis of GVHD [3, 5].

Cardiovascular risk factors and associations including dyslipidemia, hypertension, diabetes, family history, tobacco use, obesity, and prior cerebrovascular accidents, were reviewed in all 4 patients that presented with intestinal ischemia. Two of the four patients in our study did have obesity, one had morbid obesity, and two of the four had hypertriglyceridemia. Based on literature, allogeneic transplant patients are known to have substantially higher risk of developing cardiovascular risk factors compared to the normal population [6]. In a study reviewing features of metabolic syndrome in post-transplant recipients, hypertriglyceridemia was the most common feature [7]. The two patients with hypertriglyceridemia and obesity were the same two patients with laboratory evidence of microangiopathy; both died within 4 weeks following diagnosis. Despite no reports in the literature comparing cardiovascular risk factors or hypertriglyceridemia to intestinal ischemia post allogeneic transplant, our study suggests that there may be an association between the two conditions and possibly an association with poorer prognosis.

Active medications and underlying infections at the time of development of intestinal ischemia were evaluated in our study as possible predisposing risk factors. All four patients were CMV negative at the time of presentation with intestinal ischemia. CMV infections are an etiology of gastrointestinal complication post-transplant [1]; but this study gives no proposal that CMV colitis is associated with intestinal ischemia. Steroid use was reviewed since this is a common treatment of GVHD post transplantation. Three out of four of our

patients were being treated with prednisone at presentation. Steroid use was seen amongst other patients with gastrointestinal complications following allogeneic transplant in the literature [1–3].

Limitations to this report include the retrospective nature of the study and the small number of patients. There was no documentation of waist circumference in our patients and lipid documentation was not complete so the diagnosis of metabolic syndrome could not be explored. Additionally, the use of steroids in our patients may have contributed to the obesity and hypertriglyceridemia and might have also altered patient symptoms at time of presentation.

In summary based on the cases presented, young male patients may have a higher incidence of developing intestinal ischemia following allogeneic bone marrow transplantation. It appears evident that patients with acute Graft versus host Disease have an association with gastrointestinal complications; however this report shows also that patients with chronic Graft versus host Disease are at risk of developing intestinal ischemia. Obesity, hypertriglyceridemia, and TMA were identified in our study as possible risk factors for developing gastrointestinal ischemia post allogeneic bone marrow transplant. Patients with TMA in combination with cardiovascular risk factors may have the worst prognosis. Gastrointestinal ischemia may be rare but should be considered in patients following allogeneic bone marrow transplantation who present with any degree of abdominal symptoms.

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Clinical characteristics, presentation, and intervention of patients with post-transplant intestinal ischemia

Table 1

Patient no.	Gender	Age	Underlying Disease	Days post-transplant	Presentation	Surgical Intervention
1	Male	43	Acute Myelogenous Leukemia	1121	Back and epigastric pain, constipation	Partial right colectomy
2	Female	53	Myelodysplastic Syndrome	356	Shortness of breath and later developed pneumoperitoneum	Subtotal colectomy and ileostomy
3	Male	21	Hodgkin's lymphoma	775	Abdominal pain, jaundice, and malaise	Hemicolectomy
4	Male	57	Myelofibrosis	245	Lower abdominal pain, constipation, and abdominal films showed air under diaphragm	Sigmoidectomy and descending colostomy

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Table 2

Cardiovascular risk factors and associations

Patient no.	Total Cholesterol mg/dL	LDL mg/dL	HDL mg/dL	Triglycerides mg/dL	HTN	DM	CVA	BMI kg/m ²	Tobacco Use	FHx
1	259	175	53	98	Yes	No	No	43.04	No	No
2	336	137	61	776	No	No	No	31.50	No	No
3	N/A	N/A	N/A	365	No	No	No	31.27	No	No
4	131	N/A	22	84	No	No	No	22.97	No	No

LDL: low density lipoprotein HTN: Hypertension CVA: Cerebrovascular Accident FHx: Family history HDL: high density lipoprotein DM: Diabetes Mellitus BMI: body mass index