Treatment of Perianal Infection Following Bone Marrow Transplantation

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PURPOSE: Bone marrow transplantation (BMT) is often associated with profound neutropenia. Allogeneic transplant recipients also have defects in both humoral and cellular immunity and thus are subject to increased risk of serious, often life-threatening, infection even beyond the period of granulocyte recovery. The current study was undertaken to evaluate patients who required operative intervention for perianal sepsis following BMT. METHODS: The bone marrow transplant database at a single institution was used to identify all patients diagnosed with perianal infections after autologous or allogeneic BMT. Charts were reviewed in a retrospective manner. RESULTS: Over a ten-year period ending in November 1993, 963 BMT were performed at the City of Hope National Medical Center. Twenty-four patients were diagnosed with perianal infections following their transplants. Fifteen patients did not have purulent collections requiring drainage and were treated with antibiotics and supportive measures alone. Nine patients (37.5 percent) required surgical intervention between 10 and 380 days following transplantation. At the time of surgical intervention, seven patients had purulent collections and two patients had acute and chronic inflammation, tissue necrosis, and fibrosis. Of the two patients with an absolute neutrophil count less than 1,000, a purulent collection was found in one of the patients. Cultures taken from perianal abscesses were almost all polymicrobial, and the most common organisms were *Escherichia coli*, *Bacteroides*, *Enterococcus*, and *Klebsiella*. For those patients undergoing surgical intervention, mean time to complete wound closure by secondary intention was 37.6 days; five patients healed in less than 15 days, two patients healed at 93 and 114 days, and two patients had persistent, open wounds at time of death, which was unrelated to their perianal disease. Five patients were receiving systemic steroids at time of surgical intervention; this did not appear to affect time to wound healing. CONCLUSIONS: Perianal infections are a rare complication of BMT. Majority of these infections are polymicrobial, and organisms isolated are similar to those seen in the perianal infections of nonimmunosuppressed patients. Despite steroid use, granulocytopenia does not exclude the possible presence of purulent collections, and clinical examination should guide the decision for surgical drainage. In general, perianal wound healing is not prolonged in BMT patients. [Key words: Bone marrow transplantation; Perianal disease; Perianal infection; Immunosuppression]

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High-dose chemotherapy and radiotherapy requiring either autologous or allogeneic stem cell rescue is increasingly used to treat malignant diseases. Despite its overall success, serious morbidity and potentially fatal complications can result following transplantation. Posttransplant complications include graft rejection, acute and chronic graft-*versus*-host disease, posttransplant immunodeficiency, infection, and relapse.[1, 2]

Cytoreductive agents used in conditioning before bone marrow transplant (BMT) compromise the host in a variety of ways. These regimens damage rapidly dividing cell populations such as skin, mucosal epithelial cells throughout the gastrointestinal tract, and bone marrow stem cells. Resulting pancytopenia and damage to mucosal barriers create defects in host defenses. During the immediate posttransplantation period, severe granulocytopenia often results in development of bacterial infection, with pathogens generally arising from flora indigenous to the skin, upper airway, or gastrointestinal tract.[3]

This study specifically addresses development of perianal infection following bone marrow transplantation. Historically, the incidence of anorectal abscesses in acute leukemia has been reported as 3 to 5 percent,[4] with a mortality ranging from 45 to 78 percent.[5-7] Prior studies have described diagnosis and management of anorectal lesions and infections in patients with hematologic diseases.[4-7] More recent reports have suggested that even in the absence of fluctuance, early incision and debridement of perianal infections in leukemic patients results in reduced mortality related to sepsis.[8] Allogeneic BMT is associated with long-term immunosuppression and long-

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term risk for gastrointestinal damage with acute or chronic graft-*versus*-host disease. This prolongs the risk of infection well beyond the period of granulocyte recovery. The present study was designed to evaluate the outcome of patients who developed perianal infection following BMT.

METHODS

The City of Hope National Medical Center Bone Marrow Transplant Database was used to identify all patients diagnosed with perianal infections, either abscesses or cellulitis, following bone marrow transplantation. Charts of those patients fitting the above criteria were reviewed, and data regarding details of the transplantation regimen, symptoms, physical findings, laboratory tests, surgical management, and ultimate outcome were collected. Comparisons between groups were made using the chi-squared method.

RESULTS

Over a ten-year period ending in March 1993, 963 bone marrow transplant procedures were performed at the City of Hope National Medical Center. Twenty-four patients (2.5 percent) were diagnosed with perianal infections following their transplantation. Diagnosis of perianal infection was made on a clinical basis. Each of the 24 patients had at least three of the following: pain (24), erythema (20), tenderness (19), induration (12), fluctuance (9). Nine patients underwent surgical intervention, and seven of whom were found to have an abscess at time of surgery.

All bone marrow transplant patients undergo pretransplant conditioning with fractionated total body irradiation and high-dose chemotherapy. Patients also receive oral antibiotics for gastrointestinal decontamination before and during the period of neutropenia. None of the patients included in this review had a previous history of perianal disease or had perianal symptoms during the pretransplant induction period. The group included 17 men and 7 women (Table 1). The most common diagnosis was acute myelogenous leukemia.

Onset of symptoms ranged from 2 to 375 (mean, 86) days following BMT. At time of surgical consultation, 13 patients had an elevated temperature (>38°C). Incidence of fever in those patients with and without abscess was similar. Abcesses tended to accompany perianal symptoms primarily in patients who were several months post-BMT (Table 2). In addition, patients with abscesses were more likely to have progressed beyond the initial post-BMT period of neutropenia (Table 2). Clinical impression of perianal fluctuance was highly sensitive in predicting abscess (Table 2). In general, radiographic studies were not used to diagnose extent of disease or select patients for operative intervention. None of the patients in the series had signs or symptoms of graft-*versus*-host disease at time of evaluation for perianal symptoms.

Table 1.
Demographics

Sex	
Male	17
Female	7
Diagnosis	
Acute myelogenous leukemia	10
Acute lymphocytic leukemia	5
Chronic myelogenous leukemia	4
Non-Hodgkin's lymphoma	2
Hodgkin's disease	2
Myelofibrosis	1

The 15 patients who did not undergo surgical incision and drainage were treated with broad-spectrum antibiotics, warm compresses, sitz baths, and analgesics. Fourteen patients had complete resolution of symptoms within 8 to 47 (mean, 22) days. One patient died of progressive malignancy 75 days following onset of perianal symptoms, with a persistent fistula-in-ano but no perianal sepsis at time of death.

Leukocyte count at time of operative intervention ranged from 200 to 28,800/mm^3 (mean 7,200; Table 3). Two patients had an absolute neutrophil count of less than 1,000/mm.^{3} One of these patients had chronic inflammation at operation, and the other had a purulent collection.

Overall, seven patients who underwent surgical exploration had purulent collections, whereas the remaining two had induration and inflammation only. Operative cultures were polymicrobial in most instances with typical gastrointestinal flora, including *Escherichia coli, Bacteroides, Enterococcus,* and *Klebsiella.* One wound culture grew *Streptococcus viridans.* Surgical management of those patients with abscesses consisted of incision and drainage. In addition, two patients required a diverting colostomy because of extensive perianal involvement and the need for wide drainage. One of these patients underwent wide incision of the perianal region with a diverting colostomy but was found to have only cellulitis without abscess. This patient ultimately died as the result of sepsis and multisystem organ failure 55

Table 2.
Presentation

	Mean Days from BMT to Onset of Symptoms	Mean WBC at Onset of Symptoms ($\times 10^3$)	Elevated Temperature >38°C	Fluctuance	Mean Days to Resolution of Symptoms
Abscess (n = 7)	212	8.7	3	7	38
No abscess (n = 17)	34	1.1	10	2	22
	$P < 0.001$	$P < 0.001$	NS	$P < 0.001$	

NS = not significant; BMT = bone marrow transplant; WBC = white blood count.
* Survivors only.

Table 3.
Characteristics of Patients with Abscesses

Patient	Abscess	Age	Diagnosis	WBC ($\times 10^3$)	Days from BMT	Steroid Use	Outcome Following Incision and Drainage (days)
1	Yes	24	AML	28.8	223	No	Healed, 7
2	Yes	39	AML	7.9	102	Yes	Death, 44
3	Yes	39	AML	5	276	No	Healed,114
4	Yes	37	ALL	3.7	377	Yes	Healed, 93
5	Yes	24	ALL	8	257	Yes	Healed, 15
6	Yes	30	CML	7.4	255	Yes	Healed, 11
7	Yes	40	Myelofibrosis	0.2	7	Yes	Healed, 13
8	No	35	ALL	4	69	No	Death, 55
9	No	44	AML	0.6	25	No	Healed, 10

AML = acute myelogenous leukemia; ALL = acute lymphocytic leukemia; CML = chronic myelogenous leukemia; WBC = white blood count; BMT = bone marrow transplant.

days following surgery; death was believed to be unrelated to perianal disease. All postoperative wounds were managed with wet-to-dry gauze dressing changes and sitz baths. Mean time to complete wound closure was 38 (range, 7–114) days. Five patients healed in 15 days or less, two healed at 93 and 114 days, and two had a persistent open wound at time of death (44 and 55 days postsurgery). Use of systemic steroids did not appear to impact time from BMT to onset of symptoms, average leukocyte count at time of operation, or number of days until complete wound closure (Table 3). One of the surgically treated patients developed a delayed fistula-in-ano, which required fistulotomy. The remainder of surviving abscess patients had no long-term sequelae of their surgery.

DISCUSSION

Perianal sepsis is a rare complication of BMT for hematologic malignancy. This is despite significant gastrointestinal epithelial damage from conditioning regimens and despite the frequency with which the gastrointestinal tract is a target of acute graft-*versus*-host disease. Use of antivirals and gut decontamination with nonabsorbable antibiotics may decrease incidence of gram-negative sepsis and perianal infection early in the posttransplant course.[3] Early post-BMT sepsis is common with skin and gastrointestinal tract pathogens including *Staphylococcus epidermidis, S. viridans, Pseudomonas aeruginosa,* and enteric gram-negative bacillis as the leading causative organisms. Later in the posttransplant course when neutropenia has resolved fungal species such as *Aspergillis,* cytomegalovirus, and other opportunistic agents such as atypical mycobacterium and herpes simplex and zoster emerge as predominant infectious pathogens.[3, 9, 10]

Duration of posttransplant neutropenia can be quite variable and is affected by a number of factors. These factors include number and source of stem cells used for reconstitution, use of cytotoxic agents for graft-*versus*-host disease prophylaxis, occurrence of viral infections, and use of cytokines to stimulate recovery.[3] Circulating granulocyte number generally recovers to an adequate level within 30 days after transplantation. Although some patients may have prolonged functional granulocyte abnormalities, intensive pretransplant conditioning regimen may also

result in functional asplenia and defective opsonization in most patients for 6 to 12 months. This prolonged vulnerability to infection may be a factor in the long average time to onset of perianal symptoms in our series, of 86 days following BMT.

Clinical presentation of infection in granulocytopenic patients can easily go unrecognized unless careful surveillance is maintained. In our series, fever and rectal pain were the most common symptoms, and several had fluctuant masses by the time of surgical consultation. Importance of early diagnosis cannot be overstated in the face of multiple prior reports of rapidly progressive Fournier's gangrene in granulocytopenic patients.[11-13] Nevertheless, controversy has existed regarding management of perianal infections in the neutropenic patient. Although some have advocated conservative local therapy and have warned of the morbidity and mortality of operative intervention in this population,[5-7, 14] others have recommended the reliance on basic surgical principles to guide drainage of any infections in an enclosed space.[8, 11-13, 15] In fact, for acute leukemia patients with perianal infections, one investigator reported a mortality of 44 percent for those operatively drained *vs.* a 9 percent mortality for those managed conservatively.[14] Others have reported negligible mortality in acute leukemics who undergo drainage of perirectal abscesses.[8, 15] Our series, which includes only patients following BMT, also demonstrated no mortality related to conservative management of perianal sepsis and no mortality as a direct result of operative drainage of perianal sepsis. This supports the continued reliance on the basic surgical tenet of surgical drainage only in the presence of a clinical abscess even when treating these profoundly immunosuppressed patients.

Two patients in our series required a diverting colostomy in addition to incision and drainage because of the extent of their perianal soft tissue involvement. Both patients had leukocyte counts of less than 4,000/mm^3, and one patient was within one week of BMT. Although both of these patients ultimately died after a prolonged hospital stay, neither was thought to have died as a result of perianal sepsis. Accordingly, we believe that in the presence of severe perianal sepsis, a diverting colostomy can be performed safely, even in the period of granulocyte recovery, provided there is adequate perioperative support with antibiotics, platelets, and other blood products.

In reviewing culture results of drainage from perianal abscesses, it was not obvious that the impaired cutaneous and mucosal barriers or suppressed cellular and humoral immunity contributed to perianal infections in the BMT patient. The majority of infections were polymicrobial, and organisms were similar to those seen in perianal infections of nonimmunosuppressed patients. Purulent collections were discovered at time of operation in seven of nine patients who were taken to surgery, including one with a leukocyte count of 200/mm^3. This supports use of clinical evaluation to determine the need for drainage. It is imprudent to allow the presence of granulocytopenia to convince the consulting surgeon that abscess formation could not occur. Only one patient progressed to develop a fistula-in-ano following abscess drainage. For this reason and because of the fact that these patients are quite ill at time of operation, we do not advocate exploration for identification of the fistulous tract at time of initial drainage. Any resulting fistula-in-ano can be addressed at a later time.

In patients who survived, all wounds healed by secondary intention. Most were completely closed within 15 days. Systemic steroids did not appear to delay wound closure in this already profoundly immunosuppressed patient population.

CONCLUSION

Perianal sepsis following BMT poses a serious challenge for the consulting surgeon. Initial management should consist of analgesics, warm compresses, sitz baths, and broad-spectrum antibiotics to cover the commonly cultured organisms. Clinical examination can be used to diagnose fluctuance, and radiographic evaluation is rarely necessary. Indications for incision and drainage should not differ from those in the nonimmunosuppressed patient. In addition, profound neutropenia does not preclude abscess formation.

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