Case Report

Colonic Perforation in Graft Versus Host Disease: A Case Report

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Graft versus host disease (GVHD) is a phenomenon that occurs after allogeneic bone marrow transplants. Gastrointestinal (GI) manifestations of acute GVHD are common, but severe GI GVHD complications, such as bowel perforation, occur rarely and necessitate surgical intervention. To our knowledge, there are no recorded cases of colonic perforation resulting from GVHD with negative cultures for infectious agents such as cytomegalovirus. We present a case of large bowel perforation due to GVHD.

Key words: Graft versus host disease – Autoimmune response – Large bowel – Bone marrow transplantation – Colonic perforation

Although graft versus host disease (GVHD) is a common phenomenon after allogeneic bone marrow transplantation, it infrequently results in severe gastrointestinal (GI) complications that require surgical intervention such as small bowel perforation, obstruction, and GI hemorrhage. At present no cases of colonic perforation resulting from GVHD have been reported. We report a case of large bowel perforation resulting from GVHD after allogeneic bone marrow transplantation.

Case Report

We report the case of a 63-year-old man with chronic lymphocytic leukemia who received an HLA-matched unrelated stem cell transplant, followed by standard immunosuppression, antibiotic

prophylaxis, and filgrastim (Neupogen). About 1 month later, he developed a diffuse erythematous rash consistent with GVHD grade III, as well as new onset diarrhea. Although the skin rash responded well to immunosuppressives, the diarrhea continued to worsen. Colonoscopy findings were suspicious for severe GVHD. The mucosa of the right and transverse colon had moderate-to-severe inflammatory changes, friability, and patchy dark exudates. This was confirmed with pathologic analysis that revealed diffuse crypt dropout and mucosal erosion.

Despite *total parenteral nutrition* and maximal medical therapy, the diarrhea continued to progress. After several weeks, he had acute development of abdominal pain, distension, and tenderness to palpation, as well as fever and tachycardia. Pneumoperitoneum was present on computed tomography

Fig. 1 Computed tomography scan of the abdomen showing a large amount of free intraperitoneal air as well as wall thickening of the right colon.

scan (Fig. 1), and the patient was taken to the operating room emergently.

Exploratory laparotomy revealed fibrinous exudate and enteric contents throughout the abdomen. Inspection of the bowel demonstrated multiple perforations from the right colon to the splenic flexure. A subtotal colectomy with rectal stump and end ileostomy were performed. Pathologic analysis of the colon revealed numerous 0.4 to 1.0 cm perforations. The colonic mucosa showed diffuse crypt dropout, ulceration, acute inflammation and perforation, consistent with severe GVHD (Fig. 2). The small bowel and appendix also showed features of severe GVHD.

Postoperatively, the patient was brought to the surgical intensive care unit in critical condition, and the patient slowly improved with supportive care. He was discharged to a rehabilitation facility approximately 1 month later.

Discussion

GVHD is a phenomenon that occurs after allogeneic bone marrow transplants, in which transplanted lymphocytes react against HLA antigens in the recipient causing tissue destruction in the immuno-compromised host. In 1966, Billingham¹ described the three requirements for developing GVHD: the graft must contain immunologically competent cells,

Fig. 2 Histology: focal crypt epithelial apoptosis architectural distortion.

the host must possess antigens not present in the donor graft, and the host must be incapable of mounting an effective immune response against the donor. When GVHD occurs within the first 100 days after bone marrow transplantation, it is classified as acute GVHD. Conversely, after transplantation day 100, GVHD is classified as chronic GVHD. Among patients receiving marrow from an HLA-identical sibling, the incidence of acute GVHD ranges from 35% to 45%.²⁻⁴

GVHD primarily affects the skin, liver, and GI system. Within the GI system, GVHD usually affects the ascending colon, cecum, and terminal ileum.^{5,6} Intestinal manifestations of GVHD occur in 20% to 30% of all patients undergoing allogeneic bone marrow transplants.⁷ Typical GI manifestations of acute GVHD include abdominal pain and cramps, anorexia, diarrhea, vomiting, and GI bleeding. Severe GVHD complications include small bowel perforation, obstruction, and GI hemorrhage.^{5,6}

Although clinical history may be straightforward, biopsy remains the gold standard for diagnosis of acute intestinal GVHD.⁸ Thompson *et al*⁹ advocate for sigmoidoscopy and biopsy for patients at risk for GVHD with diarrhea. Pathologic features are thought to be due to cell-mediated cytotoxicity and mostly involve the mucosal crypts. Mild disease is characterized by focal crypt epithelial apoptosis and reactive changes in the surface epithelium with mucin depletion. Moderate disease may have crypt abscesses. Severe disease may show more extensive crypt cell necrosis, architectural distortion, and apoptosis in the lamina propria.^{10,11} In addition, infection with cytomegalovirus (CMV) may confound the

diagnosis, as it affects the same patient population and can have an indistinguishable presentation. It is advisable to exclude CMV infection by either biopsy or serology.

Treatment of acute GVHD typically includes administration of immunosuppressive drugs such as steroids, cyclosporine, tacrolimus, or methotrexate. More recently, novel therapies have become available, including psoralen-enhanced UVA irradiation (PUVA), extracorporeal PUVA, antibodies against interleukin-2 and tumor necrosis factor- α , thalidomide, octreotide, and mesenchymal stem cells. Further trials need to be conducted before acceptance of these newer therapies.¹²

Despite medical therapy, some patients may develop severe complications as a result of GVHD. Severe GI complications include small bowel perforation, obstruction, and GI hemorrhage.^{5,6,13–15} In a review of 36 cases of GI GVHD, Chirletti *et al*¹⁴ document 7 patients with GI emergencies, 3 of which required surgery. Four of the 7 patients experienced severe GI bleeding and 3 had acute peritonitis. One of the 3 with acute peritonitis had an ileal perforation. Another had microperforations in the cecum and left colon; however, CMV was not ruled out in this patient. Gavel *et al*¹³ and Gassas *et al*¹⁶ document cases of obstruction resulting from GI GVHD. In a larger review of 63 patients with GI GVHD, Irani *et al*⁶ found that only 1 patient required surgical intervention for multiple dilated loops of small bowel; however, no complication, such as hemorrhage, obstruction, or perforation, was found.

Bowel perforation is one of the most infrequent, yet severe complications of GVHD necessitating surgical intervention.^{15,16} In the present study we record a case of large bowel perforation due to GVHD. To our knowledge, there are no recorded cases of colonic perforation resulting from GVHD with negative cultures for infectious agents such as CMV. Oncologists should thus be aware of the possibility of large bowel perforation after bone marrow transplantation as this complication, along with bowel obstruction and severe GI bleeding, is a surgical emergency.

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