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Colonic complications following human bone marrow transplantation



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ABSTRACT

Background: Human bone marrow transplantation (BMT) becomes an accepted treatment of leukemia, aplastic anemia, immunodeficiency syndromes, and hematologic malignancies. Colorectal surgeons must know how to determine and manage the main colonic complications.

Objective: To review the clinical features, clinical and pathological staging of graft vs host disease (GVHD), and treatment of patients suffering with colonic complications of human bone marrow transplantation.

Patients and methods: We have reviewed the records of all patients that received an allogeneic bone marrow transplant and were evaluated at our Colon and Rectal Surgery department due to gastrointestinal symptoms, between January 2007 and January 2012. The study was carried out in patients who developed colonic complications, all of them with clinical, histopathological or laboratory diagnosis.

Results: The study group was constituted by 77 patients, 43 male and 34 female patients. We identified colonic complications in 30 patients (38.9%); five patients developed intestinal toxicity due to pretransplant chemotherapy (6.4%); graft vs. host disease was present in 16 patients (20%); 13 patients (16.8%) developed acute colonic GVHD, and 3 (3.8%) chronic GVHD. Infection was identified in 9 patients (11.6%).

Conclusions: The three principal colonic complications are the chemotherapy toxicity, GVHD, and superinfection; the onset of symptoms could help to suspect the type of complication (0–20 day chemotherapy toxicity, 20 and more GVHD), and infection could appear in any time of transplantation.

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Complicações do cólon após transplante de medula óssea humana

R E S U M O

Palavras-chave:

Complicações do colón
Transplante de medula óssea humana
Superinfecção

Experiência: O transplante de medula óssea humana (MOH) passou a ser um tratamento adotado para leucemia, anemia aplástica, síndromes de imunodeficiência e neoplasias hematológicas. Cirurgiões colorretais devem saber como determinar e tratar as principais complicações do cólon.

Objetivo: Revisar as características clínicas, estadiamentos clínico e patológico da doença do enxerto versus hospedeiro (DEVH) e o tratamento de pacientes padecendo com as complicações colônicas do transplante de medula óssea humana.

Pacientes e Métodos: Revisamos os registros de todos os pacientes que receberam um transplante de medula óssea alogênica e foram avaliados em nosso Departamento de Cirurgia do Cólon e Reto em função de sintomas gastrointestinais, entre janeiro de 2007 e janeiro de 2012. O estudo teve por base os pacientes que desenvolveram complicações do cólon, todos com diagnóstico clínico, histopatológico ou laboratorial.

Resultados: O grupo de estudo foi constituído por 77 pacientes, sendo 43 homens e 34 mulheres. Identificamos complicações do cólon em 30 pacientes (38,9%); cinco pacientes exibiam toxicidade intestinal por quimioterapia antes do transplante (6,4%); DEVH estava presente em 16 pacientes (20%), 13 pacientes (16,8%) foram acometidos por DEVH colônica aguda três pacientes (3,8%) DEVH crônica. Infecção foi detectada em 9 pacientes (11,6%).

Conclusões: As três principais complicações do cólon são: toxicidade por quimioterapia, DEVH e superinfecção. O surgimento dos sintomas poderia ajudar a levantar suspeitas sobre o tipo de complicação (0-20 dias, toxicidade por quimioterapia; 20 ou mais dias, DEVH). Infecções podem ocorrer em qualquer momento do transplante.

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Introduction

During the 1980s the human bone marrow transplantation (BMT) became from experimental therapy for end-stage patients to its current place as an accepted treatment of leukemia, aplastic anemia, immunodeficiency syndromes, and hematologic malignancies.¹⁻⁵ The long-term disease-free survival for untransfused patients with severe aplastic anemia is up to 80% and for patients with acute nonlymphoblastic leukemia transplanted in first remission it approaches 60%,^{1,2} therefore the number of allogeneic bone marrow transplantations performed worldwide increases exponentially.^{6,7}

BMT may cause intestinal damage by three mechanisms: toxicity from pretransplant chemoradiation, graft-versus-host disease (GVHD), and infection in the immunosuppressed host. The main late complication of allogeneic bone marrow transplant is the GVHD.³⁻⁵ Intestine, skin, lungs,⁸ liver and lymphoid organs are the main target organs in GVHD.⁴ About 30-50% of allogeneic marrow recipients will develop intestinal GVHD,^{2,9-12} with a fatal outcome in up to 15%.¹¹ Gastrointestinal tract involvement is frequently the most severe and difficult to treat.⁴

Allogeneic bone marrow transplantation is now widely practiced, and therefore, specialist evaluations for a multidisciplinary team are now demanding; gastroenterologists and colorectal surgeons must know how to determine and manage these main colonic complications. The aim of this study is review the clinical, laboratorial, endoscopic

and pathological features, and treatment of patients suffering with colonic complications of human bone marrow transplantation.

Patients and methods

We have reviewed the records of all patients that received an allogeneic bone marrow transplant and were evaluated at our Colon and Rectal Surgery department due to gastrointestinal symptoms, between January 2007 and January 2012. The study was conducted only in patients who developed colonic complications, all of them with clinical, histopathological or laboratory diagnosis.

All patients were studied and admitted by the Hematology department and Bone Marrow Transplant Clinic due to variable hematological diseases; they were evaluated by histocompatibility typing to select a suitable marrow donor using peripheral blood leukocytes to define the loci of the human leukocyte antigen (HLA) complex, and received a preparative regimen for transplantation with busulfan (16 mg per kilogram) q.i.d, over a 4 day period, plus cyclophosphamide (120 mg per kilogram) single dose, over a 2 day period, (BUCY 2 regimen) to eradicate malignant cells as well as prevent rejection of the donor marrow. The patients were placed in laminar air-flow isolation room, and all of them received prophylactic therapy with methotrexate and cyclosporine to modulate acute GVHD. A day after the preparative regimen that the patients underwent for marrow infusions was "day zero" from

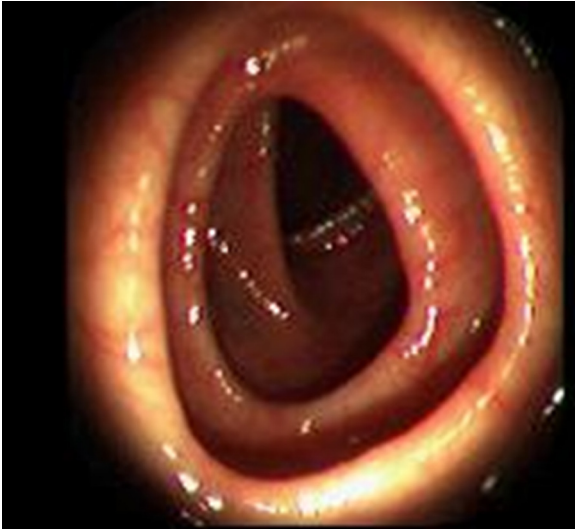


Fig. 1 – Normal appearance of the colonic mucosa in colonoscopy.

which all subsequent events were dated, as well as the onset of digestive symptoms.

Results

The first BMT done in our hospital was in 1995, and its application has been increasing with time. We reviewed the records of 77 patients with allogeneic transplants performed between 2007 and 2012, who presented digestive symptoms, and were submitted to evaluation at the Colon and Rectal Surgery department. The study group was constituted by 43 male and 34 female patients, with ages from 16 to 50 years, mean 31.3. The indication for transplant was: in 38 patients Chronic Myelocytic Leukemia, in 20 patients Acute Myelogenous Leukemia, in 8 patients Acute Lymphoblastic Leukemia, in 7 patients Myelodysplastic Syndrome, and in 4 patients Aplastic Anemia.

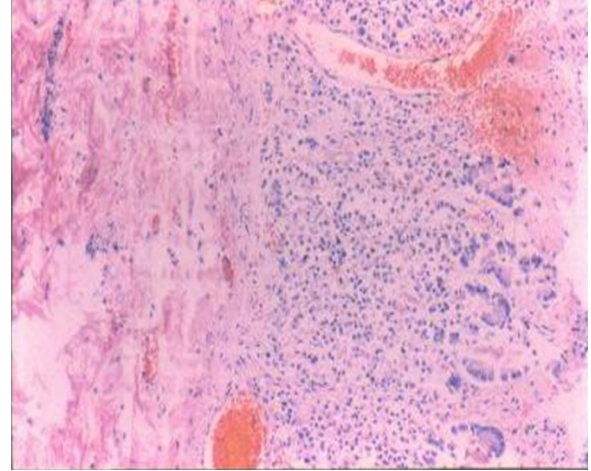


Fig. 2 – A rectal biopsy showing diffuse destruction of crypts as effect of conditioning chemotherapy.

HLA was 100% identical in 65 patients. We identified colonic complications in 30 patients (38.9%) that are presented as follows.

Chemotherapy toxicity

Five patients developed intestinal toxicity due to pretransplant chemotherapy (6.4%); all of them presented high watery diarrhea, anorexia, nausea, and crampy abdominal pain. The symptoms onset was from day 5 to day 12. At physical examination with generalized colic abdominal pain, there was increase in frequency of intestinal peristalsis but no signs of peritonitis, colonic mucosa appeared normal in the endoscopic studies (colonoscopy or rectoscopy) and biopsies reported only chemotherapy toxicity (Figs. 1 and 2) with regeneration at day 16–20, no pathogens were isolated from stools. All patients were treated conservatively with fluid and electrolyte replacement and prophylactic therapy with metronidazole 500 mg IV t.i.d plus ciprofloxacin 500 mg IV



Fig. 3 – Patchy erythema and inflammation of the colonic mucosa.

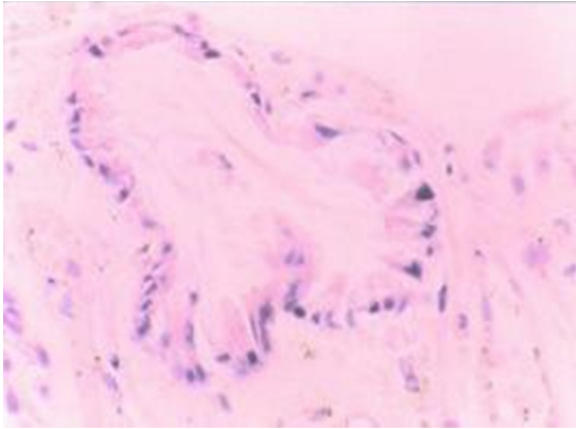


Fig. 4 – Colonic biopsy showing apoptosis (cell necrosis in crypts), flattening epithelium, and total epithelial denudation.

b.i.d. Resolution of the symptoms was achieved in 2–3 weeks approximately.

Graft vs. host disease

Graft vs. host disease was present in 16 patients (20%), 13 patients (16.8%) developed acute colonic GVHD, and 3 (3.8%) chronic GVHD; symptoms were developed from day 20 to day 182, characterized by nausea, anorexia, vomiting, crampy abdominal pain, profuse diarrhea with mucous, and occasionally lower gastrointestinal (GI) bleeding, with abdominal distension without peritoneal signs.

4 patients developed skin (maculopapular skin rash on the trunk, palms, soles and ears) and hepatic manifestations (jaundice and serum transaminase increase). All patients underwent colonoscopy with findings of patchy erythema and inflammation of the mucosa through the colon (Fig. 3), most frequently in ascendant colon, and ileocecal valve area; histopathology study of the mucosal biopsies confirmed GVHD (Fig. 4). All patients were treated with fluid, an electrolyte replacement, and steroid therapy was initiated with methylprednisolone 0.5–2 mg/kg/day in all patients; 2 patients with lower GI bleeding received subcutaneous injection of somatostatin analogs (octreotide, 50 µg t.i.d), and 8 of the patients with acute GVHD received total parental nutrition (TPN) to maintain intestinal rest. Bleeding stopped spontaneously in all patients. Eight patients received as a complement of their systemic immunosuppression an empiric treatment with 9 mg oral budesonide in a daily single dose for 3 weeks. One patient developed acute respiratory failure and pulmonary hemorrhage secondary to pulmonary GVHD and died on the 59th posttransplant day.

The 3 patients with chronic GVHD were treated on an outpatient basis with oral prednisone.

Infection

Infection was identified in 9 patients (11.6%). 5 patients with cytomegaloviral enterocolitis (CMV) corroborated



Fig. 5 – Colonoscopic appearance of CMV infection. Ulcers vary from punctuate lesions to coalescing deep ulcers.

by endoscopic appearance and histopathological studies (Figs. 5 and 6), identifying the characteristic intranuclear inclusion bodies of CMV; 3 patients developed pseudomembranous colitis (*Clostridium difficile*) showing the typical presence of the adherent so-called pseudomembranes at the colonoscopy (Fig. 7), and 1 patient was with superinfection by *Shigella*, obtained in fecal cultures and with edema and multiple small ulcerations in the colon mucosa in the colonoscopy (Fig. 8). The onset of symptoms began on day 8 onwards. All patients were initially treated with the same general indications, fluid and electrolyte replacement, etc., and then the specific treatment for each condition, ganciclovir 5 mg/kg/b.i.d for CMV, vancomycin 500 mg IV q.i.d or metronidazole 500 mg IV t.i.d for pseudomembranous colitis and ciprofloxacin 500 mg IV b.i.d for the patient with *Shigella* superinfection.

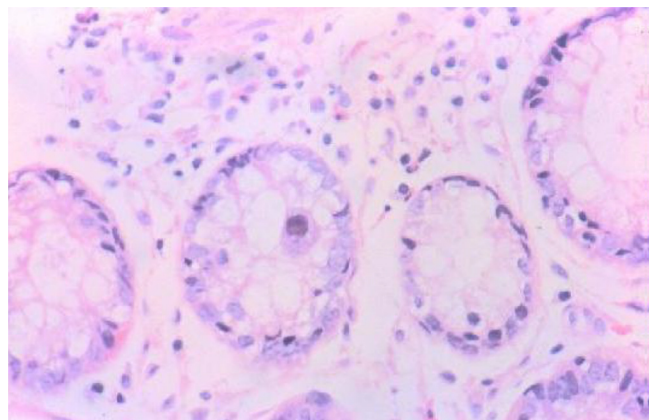


Fig. 6 – Photomicrograph of a colonic biopsy obtained by endoscopy. Viral inclusion in colonic mucosal cells.

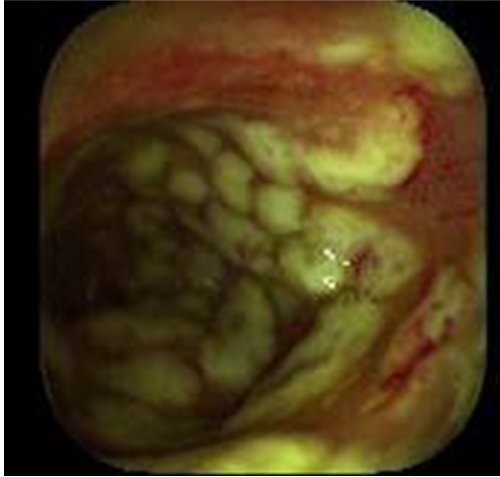


Fig. 7 – Mucosal edema and presence of pseudomembranes in colonoscopy.

Discussion

The human bone marrow transplantation has become an accepted treatment for patients with several hematological disorders.^{1,13} The marrow is given by intravenous infusion and within 2–4 weeks the marrow cellularity and peripheral counts increase as the donor graft becomes functional.

Diagnosis and treatment of the gastrointestinal complications can be extremely complex, as one must decide whether a symptom is due to the conditioning regimen toxicity, GVHD, infection or a combination of causes.¹² Diarrhea is a common and serious symptom of this complications.^{7,10,14}

Chemotherapy toxicity must be suspected when the patient develops intestinal symptoms from day zero to day 20. Previous studies have shown that diarrhea caused by cytoreductive therapy has resolved by day 20 in almost all

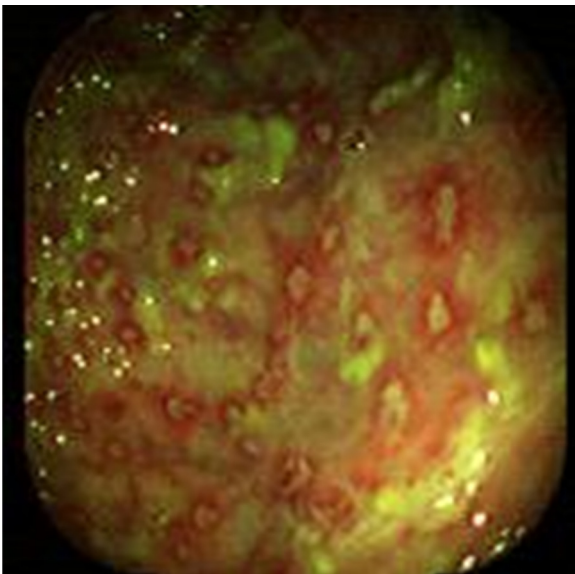


Fig. 8 – Mucosal edema and ulceration in superinfection by *Shigella*.

patients. When chemotherapy is combined with total body irradiation we observe diffuse mucosal abnormalities within 10 days of transplantation, and necrosis of intestinal crypts, with atypia of crypt cell nuclei; biopsy specimens taken 16–20 days after transplantation showed evidence of regeneration. Venocclusive diseases of the liver and pericentral hepatocyte necrosis have been related to chemoradiation therapy and can even produce fulminant hepatic failure. The additive or possible synergistic effect of radiation in inducing organ damage during allogeneic GVHD is well recognized.⁵ Thus radiation has been reported to reduce survival time, induce GVHD at earlier time, enhance the intensity of GVHD, or increase the incidence of GVHD.¹⁰

Acute GVHD usually starts 4–5 weeks after marrow transplantation, and consists of dermatitis, enteritis, and liver disease. Patients with intestinal involvement have profuse diarrhea usually watery with a mucoid appearance, crampy abdominal pain, nausea, anorexia, and blood in their stools; the patients may have abdominal pain with sometimes peritoneal signs probably for transmural edema and inflammation of the small intestine⁴; GVHD can involve upper gastrointestinal tract, characterized by the nonspecific symptomatology of nausea, vomiting, bloating, and food intolerance¹⁵; in colon the most frequent localization of disease is in the ascending colon, but all regions of the colon have been reported to be involved. The basic histopathological feature of acute GVHD, which occurs in the first 100 days posttransplant, is necrosis of individual cells in the regenerating compartment of the mucosa.¹⁶ The basic pathology of chronic GVHD is fibrosis of the submucosa and subserosa which occurs generally after 3 months posttransplant, therefore mucosal biopsy is of limited usefulness in the diagnosis of chronic GVHD.¹⁶

Antimicrobial chemotherapy targeted to intestinal anaerobic bacteria in marrow transplant recipients reduces the severity of acute GVHD and supports the theory that the intestinal anaerobic bacterial microflora plays a significant role in the pathogenesis of acute GVHD after human marrow transplantation.^{17,18}

Endoscopic examination is usually safe for patients with GVHD. It can give critical information on clinical decision making when the histology is discordant with clinical presentation.^{19,20} The endoscopic appearance of GVHD ranges from normal mucosa to erythema, mucosal sloughing, or patchy erosions.^{7,10,21,22} Biopsy has been shown to be accurate in the identification of GVHD.^{7,11}

Histopathologic findings of GVHD are: colonic wall inflammatory infiltrate of mature and activated lymphocytes, macrophages, and neutrophils.^{10,23} Crypt dropout and necrosis (apoptosis) are the characteristic histological lesions (“exploding crypt cells”) and are present only in relatively intact mucosa; when the disease is advanced with total mucosa denudation the biopsy is less specific.^{1,12} GVHD in biopsy samples can be histologically graded as follows: Grade I: single cell necrosis and apoptosis; Grade II: evidence of epithelial damage by crypt/glandular abscess, epithelial flattening or crypt/glandular dilation; Grade III: dropout of one or more crypts/glands, and Grade IV: total epithelial denudation.²⁴

Radiographic evaluation can show occasional pneumatosis in small intestine,²⁵ mucosal and submucosal edema, and mucosal ulcerations and thickened colonic walls in the

barium enema, be aware that these findings can be also caused by cytomegalovirus enteritis or radiation injury, making impossible the differentiation on the basis of radiographic findings alone.²⁶ Jones et al.¹¹ used CT scan to evaluate the extent of gastrointestinal involvement; their findings include wall thickening, bowel fold enlargement, bowel dilatation, luminal narrowing, mesenteric nodes, and increased density in mesenteric fat compatible with inflammation, with scans obtained 16–25 days after initial scans.

The standard treatment of acute GVHD, irrespective of site, is corticosteroids and/or immunosuppressive agents.^{4,27} Operative intervention is rarely therapeutic, but surgery can be performed for complications of intestinal graft-versus-host disease not responding to medical therapy.^{4,28} Mature surgical judgment is necessary to avoid unnecessary and very dangerous operations.

Perianal infections are a rare complication of BMT, these infections are polymicrobial, and organisms isolated are similar to those seen in the perianal infections of nonimmunosuppressed patients.²⁹

The finding in the stools of fungal elements, parasites, pathogenic bacteria or viruses suggests superinfections complicating BMT.

Cytomegalovirus infection has been documented in 40–50% of patients undergoing BMT.³⁰ Not only immunoglobulin and antivirals such as acyclovir are proposed medical treatments,³⁰ but also surgical treatment has been reported in complications.³¹ Diagnosis is made histologically with the presence of typical or atypical cytomegalovirus inclusions, because the morphologic features are similar with GVHD.³² Massive hematochezia secondary to graft-versus-host disease and cytomegalovirus infection has been reported.³³ Other viral infections reported in BMT patients are herpes simplex virus infection. Only six patients with intestinal infection due to herpes virus (colitis in all of the cases) have been reported in the literature.³⁴

Cryptosporidia are protozoal parasites that can infect the gastrointestinal tract of man. In immunologically normal subjects the disease is self-limited, resolving in five to ten days. Cryptosporidium infection has been reported following BMT as a cause of diarrhea.³⁵ The proposed treatment for this condition includes metronidazole and nitazoxanide which have been shown to improve symptoms.³⁶

Eosinophilic colitis is a rare inflammatory disease characterized by eosinophilic infiltration of the colon and peripheral blood eosinophilia. Eosinophilic colitis has been reported in association with allogeneic bone marrow transplantation.³⁷

Conclusions

As the practice of bone marrow transplant is increasing, it is almost certain that a gastroenterologist or colorectal surgeon should be faced to this type of colonic complications developed in consequence. We must know how to identify and treat them opportunely with the assistance of a multidisciplinary team to offer a good outcome to the patient.

The three principal colonic complications are the chemotherapy toxicity, GVHD, and superinfection; the onset of symptoms is important, and could help to suspect

the type of complication (0–20 day chemotherapy toxicity, 20 and more GVHD, infection could appear in any time of transplantation) and plan the type of treatment.

Conflicts of interest

The authors declare no conflicts of interest.

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