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CASE REPORT

Acute colonic pseudo-obstruction following allogeneic stem cell transplantation successfully treated by neostigmine

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Abstract

Acute colonic pseudo-obstruction (ACPO), also known as Ogilvie's syndrome, is a rare clinical syndrome of massive large bowel dilatation without mechanical obstruction, which may cause significant morbidity and mortality. Treatment focuses on decompressing a severely dilated colon. The proposed theory that this severe ileus results from an imbalance in the autonomous regulation of colonic movement supports the rationale for using neostigmine, a reversible acetylcholinesterase inhibitor, in patients who failed conservative care. Although gastrointestinal complications are frequent following allogeneic stem cell transplantation (SCT), the incidence of ACPO in a transplant setting is unknown and, if not vigilant, this adynamic ileus can be underestimated. We describe the case of a patient with myelodysplastic syndrome undergoing non-myeloablative allogeneic SCT from a partially human leukocyte antigen-mismatched sibling donor, and whose clinical course was complicated by ACPO in the early post-engraftment period. The ileus was not associated with gut graft-versus-host disease or infectious colitis. After 3 days of conservative care, intravenous neostigmine (2 mg/day) was administered for 3 consecutive days. Symptoms and radiologic findings began to improve 72 hours after the initial injection of neostigmine, and complete response without any associated complications was achieved within a week. Thus, neostigmine can be a safe medical therapy with successful outcome for patients who develop ACPO following allogeneic SCT.

Key Words Acute colonic pseudo-obstruction, Ogilvie's syndrome, Myelodysplastic syndrome, Allogeneic stem cell transplantation

INTRODUCTION

Acute colonic pseudo-obstruction (ACPO) presenting with massive abdominal dilatation, also known as Ogilvie's syndrome, is characterized by a clinical syndrome of symptoms, signs, and radiographic findings indicating massive colonic dilatation in the absence of mechanical obstruction [1, 2]. This severe adynamic ileus usually develops in hospitalized patients associated with critical medical and surgical conditions [1, 3]. Early recognition and appropriate management are critical to minimize morbidity and mortality mainly due to ischemia and perforation, which have a reported mortality rate of approximately 40% [1, 4].

While the pathophysiology of ACPO is still unclear, proposed mechanisms suggest it results from an imbalance between sympathetic and parasympathetic innervations in the regulation of colonic motor activity [1, 2, 5]. Several studies have demonstrated the release of endogenous opioids as a result of surgical stress or as part of the anti-inflammatory response [1]. Although data are lacking, in an allogeneic stem cell transplantation (SCT) setting, excessive use of opiate analgesics or laxatives, gastrointestinal (GI) mucositis, or endogenous opioid release itself may all have some effect in the development of ACPO.

Herein, we describe a patient with myelodysplastic syndrome who underwent non-myeloablative allogeneic SCT complicated by ACPO in the early post-engraftment period and who was successfully treated with neostigmine.

CASE REPORT

A 57-year-old woman with myelodysplastic syndrome re-

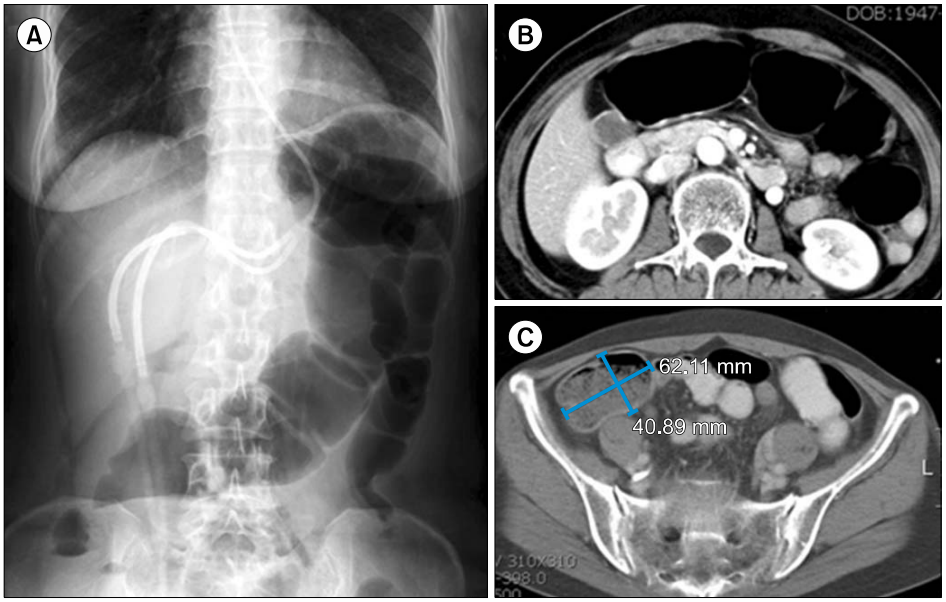

Fig. 1. Plain abdominal radiograph on day +20 post-transplant reveals the presence of a dilated colon **(A)**. A gaseous dilated transverse and ascending colon is shown on a computed tomography scan **(B)** obtained on the same day (day +20). There was no evidence of mechanical obstruction, bowel wall thickening, or abnormal enhancement. The blue lines indicate cecal diameter **(C)**.

lapse was referred to our center in September 2004. She was diagnosed with refractory anemia with excess blasts-2 (RAEB-2) (International Prognostic Scoring System intermediate-2 risk) 6 months earlier [6, 7], and was administered 2 cycles of chemotherapy with topotecan and cytarabine. Four months after achieving complete remission [8], the patient experienced relapse and the disease status was RAEB-1 at the time of referral. While preparing for allogeneic SCT from a partially human leukocyte antigen-mismatched sibling (DR locus) donor, she underwent intensive chemotherapy with idarubicin, fludarabine, cytarabine, and granulocyte-colony stimulating factor.

In December 2004, the patient underwent allogeneic SCT with a reduced-intensity conditioning regimen: 30 mg/m^2 fludarabine from day -6 to -2 and 3.2 mg/kg Busulfex on days -4 and -3. Considering one DR locus allele mismatch, Campath-1H 20 mg was added from day -7 to -5 and cyclosporine was used for graft-versus-host disease (GVHD) prophylaxis. Her performance status was 1 according to the Eastern Cooperative Oncology Group scale and the blast count at SCT was 6%, consistent with that for RAEB-1. In accordance with our center's policy, postcentrifugal plasmapheresis was performed for the donor-recipient ABO major mismatch for 3 consecutive days before the conditioning. After the infusion of the peripheral blood stem cell graft containing 6.4×10^6/kg CD34$^+$ cells and 25.5×10^7/kg CD3$^+$ cells, neutrophil engraftment occurred on day +12.

On day +16, the patient complained of abdominal pain and had watery diarrhea of more than 500 mg a day (>5 times/day). She had no skin lesions or hyperbilirubinemia. Blood cell counts showed: 7.86×10^9/L white blood cells, with 7.51×10^9/L absolute neutrophils, 156×10^9/L platelets, and 10.8 g/dL hemoglobin. C-reactive protein level was elevated and the patient developed mild fever. Other laboratory results, including the cytomegalovirus (CMV) antigen assay, were all negative. Stool toxin assay for *Clostridium difficile* was negative and the standard bacterial stool culture did not detect any causative pathogen. On the next day, sigmoidoscopy was performed to obtain random mucosal biopsies and intravenous (IV) prednisolone therapy at 2 mg/kg was initiated because gut GVHD was clinically suspected. An abdominal radiograph obtained after sigmoidoscopy revealed non-specific findings. The diarrhea had then stopped, and instead, constipation with highly aggravated diffuse abdominal pain had developed. On day +20, large bowel dilation and paralytic ileus was observed on an abdominal radiograph (Fig. 1A), and a contrasted computed tomography scan of the abdomen and pelvis (Fig. 1B) revealed diffuse proximal large bowel gaseous distension with the diameter of the cecum being greater than 6 cm (Fig. 1C) without any definite obstructive lesion. Colonic and rectal mucosal biopsy results revealed non-specific findings with no evidence of GVHD and the immunohistochemical stain for CMV was negative. On the basis of these findings, ACPO was suspected. Because the patient did not respond to the initial interventions, including total parenteral nutrition with hydration and rectal tube insertion, intravenous neostigmine was administered at 2 mg/day over 5 minutes on day +24, 4 days after the onset of ileus, while tapering the prednisolone. After 4 days of IV neostigmine treatment, the patient began to experience resolution of the ileus, indicated by defecation; decompression of the colon was observed on follow-up abdominal radiographs. From the next day, IV neostigmine was switched to oral pyridostigmine bromide at 60 mg/day. At 6 days after the first administration of neostigmine, complete resolution of the paralytic ileus was achieved, both clinically and radiologically (Fig. 2), without any other complication.

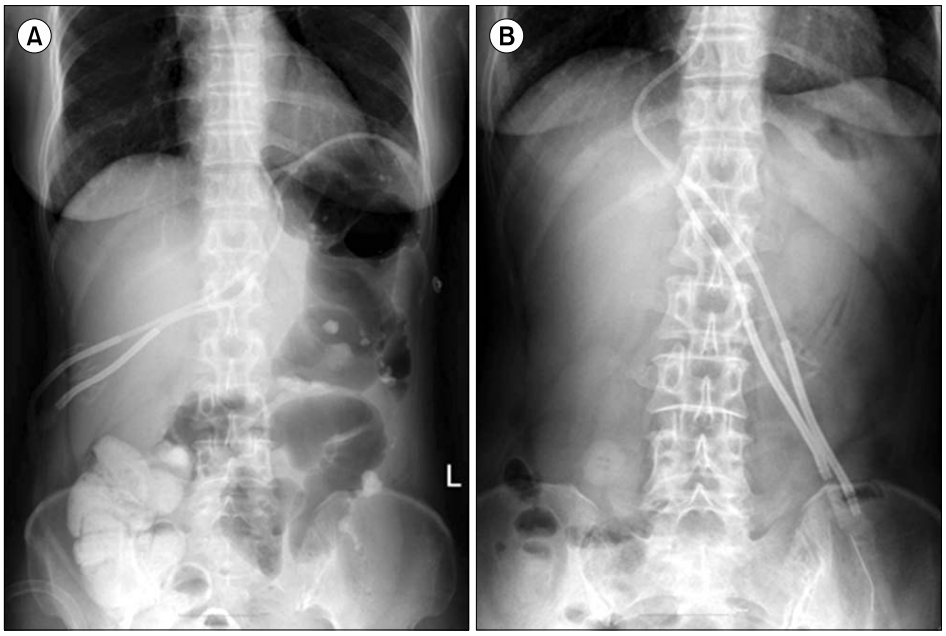

Fig. 2. Follow-up plain abdominal radiographs obtained on day +24, when neostigmine administration was initiated **(A)**, and on day +30 show complete resolution of the colonic dilatation **(B)**.

DISCUSSION

GI complications are common after allogeneic SCT for hematologic malignancies [9]. In the early post-engraftment period, the main differential diagnoses include GVHD, viral enteritis (with CMV being the leading cause), pseudomembranous colitis, and other less common causes such as pneumatosis intestinalis, and intestinal thrombotic microangiopathy. On the contrary, the incidence of ACPO after allogeneic SCT is unknown, and can only be suspected to be very rare since only a few cases have been described in the literature [10]. Moreover, unless recognized and promptly managed, ACPO could lead to a life-threatening condition. Making an accurate diagnosis can be problematic in the beginning since the majority of post-transplant patients show symptoms and signs from GI mucosal damage secondary to chemotherapeutic agents and radiation therapy used for conditioning [9, 11]; therefore, clinicians may overlook the possible clinical features of ACPO. In the present case, the patient did not have many symptoms resulting from mucosal damage except for nausea. However, soon (7 days) after neutrophil engraftment, watery diarrhea developed and IV steroids were administered for the acute GVHD, a conventional approach in an allogeneic transplantation setting. The possible effects of administration of a μ-opioid receptor agonist for symptomatic treatment and sigmoidoscopic procedures on the development of ileus were not likely causes in this case, since the patient took only 4 mg of the opioid receptor agonist. Moreover, an abdominal radiograph obtained after sigmoidoscopy did not reveal much gas accumulation related to the procedure. In recipients of allogeneic hematopoietic stem cells, usual causes of ileus include drug use (especially opiate analgesics), electrolyte imbalance (especially hypokalemia), intestinal infections (including CMV enteritis, candidal enteritis), sepsis, pancreatitis, abdominal abscess, and severe forms of acute intestinal GVHD, and should all be considered when patients present with GI symptoms [9]. Additionally, ACPO, despite its rarity, should also be included in the differential diagnosis for GI symptoms.

Initial management generally starts with correction of all potentially reversible causes, i.e. infection, hypovolemia, abnormal electrolytes, and use of drugs that may decrease bowel movements, such as narcotics and anticholinergic agents; subsequently, conservative care is performed with total parenteral nutrition and bowel decompression with nasogastric suction or sometimes with rectal tubes in cases of rectosigmoid involvement [1, 2]. A cecal diameter above 9 cm indicates the necessity to proceed with medical or endoscopic decompression of the dilated colon, although according to a systemic review, the duration and progression of colonic distention seems to be more important [2]. One study reported that a cecal diameter of >12 cm [12] and duration of distention for more than 6 days were parameters predicting increased risk of perforation [13]. Delay in decompression, especially in patients with old age or debilitating conditions, influences outcome, and the mortality rate is approximately 40% when ischemia or perforation occurs [2]. Options for non-surgical mechanical approaches include colonoscopic decompression with tube placement or percutaneous cecostomy performed through a combined endoscopic-radiologic approach [1, 2, 10]. According to retrospective series, overall colonoscopic success rates are estimated at approximately 70–80% with varying percentages of complications, although colonoscopy in ACPO is a technically difficult procedure [2]. Surgical interventions, because of the significant sequelae and mortality related to procedures, must only be considered for patients with signs of

bowel ischemia or perforation or who fail non-surgical decompression methods [1, 2, 10].

Neostigmine, a reversible acetylcholinesterase inhibitor, enhances bowel movement with colonic propulsion and accelerates transit time [3, 5]. Since its first use in 1969 by Catchpole [14], the efficacy of IV neostigmine infusion has been reported in several trials [5]. Unless patients are at risk for bradycardia and/or low systolic blood pressure (<90 mmHg), active bronchospasm, renal insufficiency, or bowel perforation, neostigmine is generally considered safe for use [1]. In our patient, despite conservative care, bowel distension persisted for more than 72 hours with aggravated abdominal pain, and there was no discernible underlying cause for this pseudo-obstruction except that she was in post-transplantation status at day +20. On day +25, 1 day after the initial neostigmine administration, preemptive ganciclovir was initiated owing to elevated CMV DNAemia titer, as detected by regular routine laboratory evaluation. Ganciclovir therapy was unlikely to have affected the outcome since CMV reactivation had occurred 1 week after the onset of GI symptoms, and immunohistochemical analysis of the colonic mucosal biopsy revealed negative results for CMV. Our patient received 2.0 mg IV neostigmine over 5 minutes for 3 days, and responded to the therapy 72 hours after the first infusion, and exhibited effective passage of stool and flatus followed by gradual relief of abdominal distension and restoration of normal peristaltic activity over the next 5 days.

In conclusion, a rare complication of ACPO following allogeneic SCT can initially manifest with only nonspecific symptoms mimicking more common complications like GVHD. In such cases, ACPO must be considered to ensure an accurate diagnosis and prompt treatment decision for colonic decompression in order to reduce mortality from bowel ischemia or perforation. Neostigmine can be safely used and is associated with successful outcome even in patients undergoing allogeneic SCT.

Authors' Disclosures of Potential Conflicts of Interest

No potential conflicts of interest relevant to this article were reported.

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