Acute Colonic Pseudo-Obstruction Caused by Mycophenolate Mofetil in a Kidney Transplant Recipient

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Abstract

Mycophenolate mofetil is a component of immunosuppressive regimens in solid-organ transplant recipients. Gastrointestinal symptoms such as nausea, abdominal pain, and diarrhea without fever are common in patients treated with mycophenolate mofetil. We treated a patient who had acute colonic pseudo-obstruction after kidney transplant that resolved after discontinuing mycophenolate mofetil. The disorder recurred soon after resuming mycophenolate mofetil, which is evidence for an association between mycophenolate mofetil and acute colonic pseudo-obstruction in this patient.

Key words: Complications, End-stage renal disease, Immunosuppression, Ogilvie syndrome

Introduction

Acute colonic pseudo-obstruction (also termed Ogilvie syndrome) is characterized by colonic distension without mechanical obstruction. This syndrome has been described in association with various operative procedures in the abdomen, pelvis, retroperitoneum, and cardiothoracic system. Several medical conditions and drugs also have been associated with acute colonic pseudo-obstruction.1

Mycophenolate mofetil is a common component of immunosuppressive treatment after kidney transplant.2-3 The most common gastrointestinal adverse events with this drug include abdominal pain and diarrhea. However, mycophenolate mofetil has been associated with several colonic disorders such as erosive enterocolitis, ischemic colitis, and cytomegalovirus colitis.4-7 However, a literature search showed no previous association between mycophenolate mofetil and acute colonic pseudo-obstruction in a kidney transplant recipient.

We treated a patient who had acute colonic pseudo-obstruction after kidney transplant. Several treatments were attempted but were unsuccessful. The disorder resolved only after discontinuation of mycophenolate mofetil. Resuming mycophenolate mofetil treatment at a lower dose was associated with recurrence of acute colonic pseudo-obstruction.

Case Report

A 52-year-old man who had end-stage renal disease of unknown cause received a living-unrelated kidney transplant in August 2004 after 1 year of maintenance hemodialysis. The transplant procedure was uneventful, and he had prompt postoperative diuresis and improvement in serum creatinine level to 132 μmol/L by postoperative day 3. The posttransplant immunosuppressive regimen included prednisolone, mycophenolate mofetil (500 mg, 3 times/d, started immediately after transplant), and cyclosporine microemulsion (started on posttransplant day 5).

On postoperative day 5, the patient complained of abdominal pain, abdominal distension, and constipation. Physical examination showed abdominal distension, increased tympany, and decreased bowel sounds. Abdominal radiographs showed a markedly distended cecum and ascending colon. Serum creatinine level was 106 μmol/L. Serum levels of electrolytes, calcium, and magnesium were normal.

All oral food and fluids were discontinued except for oral medications. He was given intravenous fluids, and a Ryle rectal tube was inserted for continuous
drainage, but he had no improvement. Abdominal radiographs on posttransplant day 10 showed increased colonic distension involving the transverse colon. There was no improvement despite treatment with erythromycin and neostigmine. Temporary cessation of cyclosporine did not affect the colonic distension but caused an increase in serum creatinine level that improved after resuming cyclosporine. The patient was discharged from the transplant center with persistent abdominal distension, constipation, and intermittent diarrhea.

The patient presented to our hospital 2 months after kidney transplant because of dysphagia, odynophagia, and progressive abdominal distension. He had nausea, flatulence, constipation, and episodes of diarrhea. He denied any vomiting, hematemesis, or melena. Current medications included cyclosporine microemulsion, prednisolone (15 mg, once daily), mycophenolate mofetil (500 mg, 3 times daily), atenolol (50 mg, once daily), amlodipine (10 mg, once daily), and trimethoprim and sulfamethoxazole (double strength, 1 tablet per day). Physical examination showed that he appeared ill and had oral thrush. Blood pressure was 105/60 mm Hg, pulse was 100/min, and temperature was 37.8°C. Abdominal examination showed generalized distension, increased tympany, and decreased bowel sounds. There was no organomegaly, and the transplanted kidney was palpable in the right iliac fossa. Chest and cardiovascular examinations were normal. Laboratory tests showed leukopenia, anemia, normal anion gap, metabolic acidosis, and increased serum creatinine level (202 μmol/L). Serum levels of electrolytes, calcium, and magnesium were normal. Abdominal radiographs showed extensive colonic dilation (Figure 1). Upper gastrointestinal endoscopy on hospital day 2 showed extensive esophageal candidiasis. Sigmoidoscopy on hospital day 4 was normal, and a rectal tube was inserted.

Treatment included intravenous fluids, nystatin, itraconazole, adjustment of cyclosporine dosage, and discontinuation of all oral food and fluids. Serum creatinine level improved (106-123 μmol/L). Abdominal distension persisted and colonoscopy showed normal mucosa with no strictures, growth, or mucosal ulceration. On hospital day 8, mycophenolate mofetil was stopped and the abdominal distension gradually improved. Abdominal radiographs on hospital day 12 showed complete resolution of colonic distension (Figure 2).

Mycophenolate mofetil was resumed 2 weeks later (250 mg, twice daily), but the colonic dilation recurred (Figure 3). The mycophenolate mofetil again was stopped, and the colonic dilation resolved within 2 days. The patient was discharged home with a modified immunosuppressive regimen (prednisolone, cyclosporine microemulsion, and azathioprine). On follow-up, he had no recurrence of abdominal distension, and graft function was stable with serum creatinine level 123 to 140 μmol/L.
Discussion

The present patient had acute colonic pseudo-obstruction after kidney transplant that resolved after discontinuation of mycophenolate mofetil.

In 1948, Sir William Heneage Ogilvie described 2 patients who had symptoms and signs of colonic obstruction without any mechanical obstruction observed on barium enema and examination at laparotomy. Both patients had malignant disease involving the celiac plexus. Since then, acute colonic pseudo-obstruction (Ogilvie syndrome) has been associated with various clinical problems in critically ill patients. The pathophysiology is unknown but may be associated with an imbalance between the sympathetic and parasympathetic nerve supply to the large bowel.

Acute colonic pseudo-obstruction occurring after kidney transplant has been well documented. In a retrospective review of 550 kidney transplants, there were 7 patients who had acute colonic pseudo-obstruction, and literature review showed 78 patients who had acute colonic pseudo-obstruction early after transplant. Obese transplant recipients (body mass index > 30 kg/m²) have a significantly increased risk of developing this syndrome.9

In another 7-year study, there were 13 adults who developed nonobstructing colonic dilation at 1 to 13 days after kidney transplant. All patients except 1 patient had poor graft function. In addition, 7 patients had right-sided perforation, including 6 patients who had nonobstructing colonic dilation; surgery within 24 hours of the perforation was associated with survival in 6 of the 7 patients, and all survivors except 1 survivor retained functioning allografts. The authors concluded that colonic pseudo-obstruction is a potential complication of poor graft function after kidney transplant, and early surgery and reduced immunosuppression are important to prevent death.10

In an 18-month prospective study with 290 kidney transplant recipients, there were 34 episodes of acute colonic ileus (30 primary and 4 recurrent episodes) in 30 recipients (10%). Acute colonic ileus was more frequent after living-donor transplant. Multivariate analysis showed that the incidence of acute colonic ileus was directly related to mean cumulative prednisone dosage. Medical therapy had a high frequency of response (77%). In 8 patients who had colonoscopy because of progression to acute pseudo-obstruction, colonoscopy was curative in 7 patients, but 1 patient developed cecal perforation after unsuccessful endoscopic colonic decompression.11

The most common gastrointestinal adverse event from mycophenolate mofetil is diarrhea without fever. In a study of colon biopsies from 20 patients who were treated with mycophenolate mofetil after kidney transplant and had diarrhea, the diarrhea was attributed to mycophenolate mofetil because there was no other demonstrable cause and the symptoms improved when the mycophenolate mofetil dose was decreased or stopped.5 The colon biopsies had prominent crypt cell apoptosis and reactive and reparative changes that were similar to changes observed in patients who have acute intestinal graft-versus-host disease; this pattern of injury was not observed in control biopsies or biopsies from transplant patients who did not receive mycophenolate mofetil.5

In a study of 26 kidney transplant recipients who had persistent diarrhea without fever, all patients except 1 patient had erosive enterocolitis and 18 patients (70%) had malabsorption.4 An infectious cause was demonstrated in 60% patients. The diarrhea was successfully treated without a change in the immunosuppressive protocol. In 9 patients, there was no infection encountered, but inflammation was noted, similar to inflammation observed with Crohn disease. These patients had a faster colonic transit time that correlated with the trough level of mycophenolic acid. Cessation or reduction of mycophenolate mofetil caused resolution of the

Figure 3. Abdominal Radiograph After Resuming Mycophenolate Mofetil
diarrhea in all patients except 2 patients. However, 2 patients developed irreversible allograft rejection and resumed renal replacement therapy, and 1 other patient required corticosteroid therapy to reverse an episode of acute rejection. The authors concluded that mycophenolic acid or a metabolite of mycophenolic acid may cause enterocolitis in infection-free kidney transplant patients similar to Crohn disease, but cessation of mycophenolate mofetil may increase the risk of developing rejection.4

Mycophenolate mofetil also has been associated with other colonic complications in kidney transplant recipients including cytomegalovirus colitis, pseudomembranous colitis, and ischemic colitis.6,7,12 The histologic findings associated with gastrointestinal complications caused by mycophenolate mofetil include a mixed pattern of mucosal injury, architectural distortion, focal cryptitis, and increased crypt apoptosis, similar to the intestinal disorder associated with graft-versus-host disease. Symptoms and histopathologic abnormalities may improve when mycophenolate mofetil is substituted with another immunosuppressive drug.13-15

In summary, the present kidney transplant recipient had acute colonic pseudo-obstruction that persisted despite several commonly used treatments. He improved only after discontinuation of mycophenolate mofetil. The causal effect of mycophenolate mofetil was confirmed by recurrence of the syndrome soon after resuming mycophenolate mofetil at a lower dose.

References