Case Report

Bloody Diarrhea with Pseudo-Obstruction of Intestine in a Renal Transplant Recipient

Cheng-Hsu Chen1,3,4, Mei-Chin Wen2, Chi-Hung Cheng1,5, Ming-Ju Wu1,6, Tong-Min Yu1, Ya-Wen Chuang1, and Kuo-Hsiung Shu1,6

1Division of Nephrology, Department of Internal Medicine
2Department of Pathology, Taichung Veterans General Hospital
3School of Medicine, China Medical University
4Department of Life Science, Tunghai University
5Department of Biotechnology, Hungkuang University
6School of Medicine, Chung Shan Medical University
Taichung, Taiwan, Republic of China

Abstract

Diarrhea is frequent in renal transplant (RTx) recipients. Differentiating among the various infectious diseases and medications which may have caused diarrhea in transplant recipients is an important challenge. Cytomegalovirus (CMV) infection is a major cause of morbidity and mortality in RTx recipients. The gastrointestinal tract, especially the colon and rectum, is the organ most frequently invaded by CMV disease. CMV colitis presents with or without fever, gastrointestinal bleeding, pseudo-obstruction, ischemic colitis and perforation. Here we report a case of profound diarrhea with acute renal failure, which progressed to neutropenic fever, thrombocytopenia, bloody diarrhea and pseudo-obstructive intestine. Colonoscopic biopsy revealed CMV colitis. The symptoms deteriorated rapidly despite ganciclovir therapy, and surgical intervention was required. The patient survived the life-threatening disease after surgery and received 3-month ganciclovir therapy without complication. High clinical suspicion of CMV disease and early colonoscopy are necessary for prompt recognition and effective medical therapy in RTx recipients presenting with diarrhea. (Acta Nephrologica 2011; 25: 132-136)

KEY WORDS: CMV colitis, cytomegalovirus infection, kidney transplantation

Introduction

Infections constitute the leading cause of morbidity and mortality during the early posttransplant period. Cytomegalovirus (CMV) infections in the immunocompetent and immunosuppressed are not rare, with worldwide seroprevalence for CMV between 60% and 100% (1). The overall incidence of symptomatic CMV disease in the transplant population ranges from 30% to 50% (2). CMV infection is determined by the state of CMV-specific immune controls and local microenvironment that causes organinvasive disease in intestines (40%), liver (20%), lungs (10%), kidneys (5%), eyes (1%) and the central nervous system (1%) (3). CMV infection of gastrointestinal tract is associated with a clinical presentation of abdominal pain, diarrhea, hematochezia and constitutional symptoms, such as fever, malaise and weight loss. It causes vasculitis and thrombosis of the bowel vessels, which result in presentation of enterocolitis, ulceration, bleeding, intestinal pseudo-obstruction and even perforation (4, 5). Severe CMV ischemic colitis is almost always fatal (6), so early detection and prompt antiviral therapy are important for patient survival. Here we report a case presented with leucopenic fever and bloody diarrhea with intestinal pseudo-
obstruction attributed to CMV colitis following renal transplant (RTx). Surgical intervention to resect the inflammatory descending colon was inevitable despite ganciclovir therapy. The patient survived this lifethreatening disease without complication.

Case Report

A 31-year-old male with end-stage renal disease (ESRD) received a full-match cadaveric renal transplant after 2 years of hemodialysis. Both donor and recipient had serological evidence of past CMV infection. The serological markers of the donor and recipient were CMV IgG (+), CMV-IgM (-) prior to renal transplantation. He did not have CMV prophylaxis following transplantation. The graft biopsy revealed acute tubular necrosis due to prolonged cold ischemic time (14.5 hrs); the delayed graft function recovered gradually after 2-week dialysis. The pre-transplant induction was methylprednisolone 500 mg, followed by initial immunosuppressive therapy consisting of tacrolimus (2 mg twice daily) adjusted to therapeutic level, mycophenoic sodium (myfortic®; 720 mg twice daily) and prednisolone (30 mg daily). The serum creatinine level (sCr) fell to 2.4 mg/dL (eGFR: 34 mL/min) on day 14. His post-transplant course was unremarkable, however, with sCr level still at 1.9 mg/dL (eGFR: 45 mL/min) in the third month.

Two weeks before admission, he suffered from watery diarrhea 7-8 times per day without fever and with poor appetite. There were no leukocytes or erythrocytes on stool examination. The result of the serology detection of Widal test was negative and the stool culture was negative for bacterial growth. The complete blood cell counts revealed leucopenia (white cell count (WBC) 3900/mm3), mild anemia (hemoglobin (Hb): 9.6 g/dL) and thrombocytopenia (Platelet 8000/mm³). The diarrhea was attributed to micophenolic acid (MPA; myfortic®) therapy and the dose of myfortic® was adjusted to 360 mg twice daily. The severity of his symptoms was not improved. The patient started suffering from periumbilical pain, bloody stool and progressively decreased urine output 4 days before admission. Level of sCr increased to 2.4 mg/dL from the prior sCr level of 1.9 mg/dL. The patient was admitted for treatment of dehydration and further evaluation to determine the cause of hematochezia.

At admission, he was acutely ill-looking, with blood pressure 127/76 mmHg, pulse rate 75/min, respiratory rate 20/min, and body temperature 38.6°C. The physical examination disclosed mild dehydration and mild diffuse abdominal tenderness without muscle guarding, rebounding pain, Cullen’s sign or Murphy’s sign. The rest of the clinical examination was unremarkable. The initial chest film and abdominal film were normal.

Three days after admission, bloody diarrhea and intermittent abdominal pain persisted after reduction of immunosuppressive agents and symptomatic management. Colonoscopy, which was performed only up to 70 cm from anus due to procedure intolerance, disclosed scattered hyperemic spots on sigmoid colon, severe hyperemic mucosa changes on descending colon, and splenic flexion (Fig. 1) on the fourth day. Empiric gancyclovir was prescribed due to suspicion of CMV colitis. Unfortunately, he suffered from severe abdominal distention and persistent aching, exacerbated with rebounding and shaking chills with fever up to 39.5°C during the night after the procedure. A CT scan of abdomen disclosed moderate wall thickening and mural edema of a short segment of bowel loop in left upper quadrant, mild air dilatation of the ascending and transverse colon and moderate fluid dilatation of small bowel in middle and lower abdomen (Fig. 2). However, the left decubitus abdominal film (KUB) found no definite intraabominal free air, besides generalized ileus. Laboratory data revealed leukocytosis (WBC: 10000/mm³; N/L: 89.5/9.2), renal graft function deterioration (sCr from 2.0 mg/dL up to 2.8 mg/dL), no elevation of antibodies of cytomegalovirus IgM (CMV-IgM) ratio: 0.23, CMV-IgG ratio: 2.85, normal liver function test, and amylase (48 U/L) level. Bowel auscultation revealed hypoactive bowel and ischemic bowel disease was suspected. Exploratory laparotomy and left hemicolecctomy were performed and an inflamed segment measuring 16 cm in length was discovered.

Gross appearance of the resected segment of the descending colon showed thickened bowel walls, and
Fig. 2. CT scan of abdomen performed after colonoscopy revealed moderate wall thickening and mural edema of a short segment of bowel loop in left upper quadrant (white arrow head), mild air dilatation of ascending and transverse colon (thin arrow), and moderate fluid dilatation of small bowel in middle and lower abdomen.

Fig. 3. (A) Segment of descending colon and splenic flexure showed multiple patches erythematous change of mucosa with mucosal swelling. The most severe site was located in splenic flexure. The serosa layer was intact in the whole colon. No other infective lesion was noted in the entire peritoneal cavity. (B) The sections of colon showed transmural acute suppurative and chronic inflammation with edema. (C) Several large cells with intranuclear and intracytoplasmic eosinophilic inclusions were noted in the mesenchymal cells of mucosa and submucosa. (D) Immunohistochemical (IHC) staining was positive for CMV inclusions.
erythematous change with diffuse hemorrhage of the mucosa (Fig. 3A). Histologically, the resection margins were viable, but involved inflammation. The sections of colon showed transmural acute suppurative and chronic inflammation with edema. There were several large cells with intranuclear and intracytoplasmic cosinophilic inclusions noted in the mesenchymal cells of mucosa and submucosa (Fig. 3B, 3C). The immunohistochemical (IHC) staining was positive for CMV inclusions (Fig. 3D). Intravenous ganciclovir therapy was employed to treat cytomegalovirus colitis for 2 weeks after operation, followed by 3-month oral maintenance therapy. He was well without other complications after surgery, and the last sCr level was 2.2 mg/dL.

**Discussion**

Diarrhea is frequent in RTx recipients. Differentiating among the various infectious diseases and medications that may have caused diarrhea in transplant recipients is an important issue and poses a considerable challenge. Drug history should be the initial step in the diagnostic approach. The blood levels after medications should be closely monitored, because both calcineurin inhibitors and MPA can cause diarrhea. MPA is a potent non-competitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH); it inhibits the de novo pathway of purine nucleotide synthesis, thus depleting intracellular guanidine nucleotides (7). Purine synthesis by salvage pathway is not quick enough to catch the high turnover rate of GI tract; therefore, a vicious cycle is created and cannot be stopped. However, blood levels of cyclosporine in a patient with diarrhea remain stable, but significantly increased levels of tacrolimus are known to cause diarrhea. Thus, tacrolimus should be carefully monitored and the dosage has to be adjusted (8).

In a recent study of Diarrhea Diagnosis Aid and Clinical Treatment (DIDACT), the stepwise management of 108 severe diarrhea (≥ 3 stools/day for ≥ 7 consecutive days) patients involved first withholding diarrhea-inducing nonimmunosuppressive drugs (9). As a rule, the treatment approach for diarrhea should be to examine the stool for bacteria, protozoa, viruses and parasites simultaneously, followed by exclusion of bacterial overgrowth by breath tests. In the present study, the remission of diarrhea was 39% after cessation of diarrhea-causing nonimmunosuppressive drugs, and treatment of infections. Such can avoid the risk of acute or chronic rejection of graft kidney by adjusting immunosuppressive regimens, which resulted in remission from diarrhea in 23% of patients in a previous study (9). If the symptoms persist with negative work-up, endoscopic assessment should then be carried out in order to reach diagnosis. Colitis is the most frequent finding. A tissue biopsy could define the cause of colon inflammation, including infection, poor blood flow to the intestine (ischemia) and chronic inflammatory bowel diseases, ulcerative colitis and Crohn’s disease. In fact, inflammation itself seems to be a predisposing factor because of the demonstrated tropism of CMV for proliferating cells of granulation tissues (10). CMV colitis is a possible complication with or without fever, gastrointestinal bleeding, and perforation. Bloody diarrhea, often with mucus, is typical of infectious colitis, but not in drug-induced colitis. Stool examination, serology test and stool culture of our patient were all negative. Colonoscopy revealed scattered hyperemic spots on sigmoid colon which should be taken as an early sign of CMV vasculitis. A pathological examination of the colon biopsy confirmed the diagnosis of tissue-invasive CMV colitis. In a previous report, the colon and rectum was the most frequent gastrointestinal site of CMV affliction in both immunocompetent and immunocompromised patients (11). CMV infection of mainly stromal and endothelial cells, rather than macrophages, is characterized by CMV inclusions. Severe CMV colitis may result in transmural involvement, hypoperfusion, intestinal pseudo-obstruction worsening to ischemic colitis, and even bowel perforation (12). CMV directly invades vascular endothelial cells to activate and proliferate vascular cells (13) causing membrane alterations that promote coagulation by the expression of adhesion molecules, which react with platelets and leukocytes (14) and result in vasculitis and vascular thromboembolism leading to ischemic colitis. Though ganciclovir was prescribed in this case, bloody stool persisted and progressed to pseudo-obstruction of intestine, which is a potentially dangerous condition with symptoms, signs, and radiologic appearance of an acute, large bowel obstruction. The medical treatment is conservative with nasogastric decompression, and neostigmine. The most serious complication of colonic pseudo-obstruction is perforation, which inevitably requires surgical intervention.

CMV infection is a major cause of morbidity and mortality in RTx recipients. Most CMV infection occurs mainly during the first three months following the transplant, but it can occur anytime after RTx. High clinical suspicion for CMV disease and early colonoscopy biopsy are necessary for prompt recognition and effective medical therapy, as most screening methods for CMV disease may be negative. Transplant clinicians must be aware of the increased risk of CMV diseases with immunosuppressive regimens, so it is crucial to maintain an optimal dosage to reduce the risk of rejection and prevent infection.

**References**

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