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**Successful treatment of ileal ulcers caused by immunosuppressants in organ transplant recipient**

Guo YW *et al*. Ileal ulcers and organ transplantation

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**Abstract**

Gastroduodenal ulcers are common in solid organ transplant patients, however multiple giant ulcers in distal ileum and ileocecal valve caused by immunosuppressants were seldom reported. Herein, we report a liver transplant recipient and a renal transplant recipient both with multiple large ulcers in distal ileum and ileocecal valve who achieved rapid ulcers healing through sirolimus or tacrolimus withdrawing and thalidomide administration. A 56-year-old man with primary hepatocellular carcinoma had received liver transplantation. Tacrolimus combined with sirolimus and prednisolone was used as anti-rejection regimen. Colonoscopy was performed because of severe abdominal pain and diarrhea at 10 mo post-operation. Multiple giant ulcers were found at ileocecal valve and distal ileum, and achieved rapid healing through sirolimus withdrawing and thalidomide administration. There was no recurrence during two years of follow-up. Another 34-year-old man with end-stage kidney disease received kidney transplantation, and was put on tacrolimus combined with mycophenolate mofetil and prednisolone as anti-rejection regimen. On the 12th week after operation, the patient presented with hematochezia and severe anemia. Colonoscopy revealed multiple large ulcers in ileocecal valve and distal ileum, with massive fresh blood accumulation. The bleeding ceased after intravenous somatostatin and oral thalidomide. Tacrolimus was withdrawn at the same time. Colonoscopy at fourth week of follow-up revealed remarkable healing of the ulcers and there was no recurrent bleeding during one year of follow-up. No lymphoma, tuberculosis, infection of cytomegalovirus, Epstein–Barr virus or fungus was found in both patients. In some post-transplantation cases with ulcers in distal ileum and ileocecal valve, sirolimus or tacrolimus should be considered as a risk factor, and withdrawing them or switching to other immunosuppressants might be effective.

**Key words:** Ileal ulcers; Liver transplantation; Kidney transplantation; Sirolimus; Tacrolimus

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**Core tip:** Ileal ulcers caused by immunosuppressants were seldom reported. Herein, we report a liver transplant recipient and a renal transplant recipient both with multiple large ulcers in distal ileum and ileocecal valve. They achieved rapid ulcers healing through sirolimus or tacrolimus withdrawing and thalidomide administration. No lymphoma, tuberculosis, infection of cytomegalovirus, Epstein–Barr virus or fungus was found in both patients. No recurrence of ulcers as well as organ rejection was noted. In some post-transplantation cases with ileal ulcers, sirolimus or tacrolimus should be considered as a risk factor because their inhibitory effects on wound healing. Withdrawing them or switching to other immunosuppressants might be effective.

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**INTRODUCTION**

Solid organ transplant recipients are susceptible to a variety of gastrointestinal (GI) complications, one of which is ulcer disease[1-5]. Most of these ulcers locate at anastomotic stoma or gastroduodenum; ulcers at intestine or colon are rare. It has been reported that besides helicobacter pylori infection and ischemia, infection of cytomegalovirus (CMV), Epstein–Barr virus (EBV), mycobacteria and fungus can contribute to ulcer disease in transplant recipients[1-5]. A few reports suggest that the use of immunosuppressant, especially high-dose immunosuppression after transplantation might correlate with impairment of gastrointestinal tract[6,7]. Herein, we report a liver transplant recipient and a renal transplant recipient both with multiple large ulcers in distal ileum and ileocecal valve who achieved rapid ulcers healing through sirolimus or tacrolimus withdrawing and thalidomide administration.

**CASE REPORT**

***Case 1***

A 56-year-old man with primary hepatocellular carcinoma received orthotopic liver transplantation in our hospital. Prior to the transplantation, he was diagnosed with chronic HBV, Child-C liver function and elevated blood glucose. No history of renal, cardiac diseases or mycobacterium tuberculosis (TB) infection was noted. He denied smoking and drinking. Tacrolimus combined with sirolimus and prednisolone was used as anti-rejection regimen. The dose of tacrolimus and sirolimus was adjusted according the drug serum concentration. The patient recovered and liver function improved to normal level. Entecavir was applied to prevent HBV reinfection.

After administration of the immunosuppressants, the patient began to develop mild peri-umbilical pain and diarrhea, which were tolerable at the time. Probiotics and antispasmodic treatment seems not so effective. At 10 mo post-operation, he was admitted to our hospital because of severe diarrhea and abdominal pain. There were 7-10 bowel movements per day, with mucous blood stool. On physical examination, blood pressure, heart rate and temperature were normal. There was slightly tenderness on peri-umbilicus area, without rebound tenderness. Complete blood count revealed a leukocyte count of 11.50 × 109/L, erythrocyte count of 4.50 × 1012/L, hemoglobin level of 121 g/L, platelet count of 295 × 109/L, neutrophils of 76.4%, lymphocytes of 16.3%. Leukocytes and erythrocytes were found in stool. The ratio of coccus to bacillus in stool was 1:9. Serum glutamic-oxaloacetic transaminase, glutamic-pyruvic transaminase, total bilirubin, BUN, creatine, and electrolytes were within normal range. Serum 1-3-β-D dextran was < 10 pg/mL. Blood and stool cultures for fungus and bacteria showed no growth. Chest CT scan revealed no lesions and serum T-SPOT.TB was negative. IgM and IgG of EB virus were negative. Abdominal enhanced CT scan showed thickness of distal ileum and ileocecal region, suggesting inflammatory lesions. The spleen slightly enlarged, muddy stones were found in the common bile duct and no enlarged lymphonodus was noted. Chronic erosive gastritis with negative helicobacter pylori infection was confirmed through esophagogastroduodenoscopy. Colonoscopy revealed multiple giant and deep ulcers in ileocecal valve and distal ileum, with polypoid hyperplasia. The length of the largest ulcer was up to 5.0 cm (Figure 1A-C). Histopathology of biopsy specimens revealed benign ulcer and chronic inflammation with non-caseous granulomas (Figure 2A, B), without signs of fungus and parasites infection. The immunohistochemical study was negative for CMV infection. EBV encoded early small RNA (EBER) was negative by in situ hybridization.

Considering sirolimus to have more gastrointestinal complications than tacrolimus in clinical application, sirolimus was firstly withdrawn. The patient was also put on oral thalidomide at a dose of 100 mg/d for two weeks and intravenous antibiotics for one week. Diarrhea and abdominal pain were gradually relieved and subsided. Colonoscopy at sixth week of follow-up revealed remarkable healing of the ulcers in ileocecal valve and distal ileum, and only two healing 2 stage ulcers were found (Figure 1D-F). No organ rejection was noted after withdrawing sirolimus. No recurrence of diarrhea and abdominal pain was noted during two years of follow-up.

***Case 2***

A 34-year-old man with end-stage kidney disease was admitted to the department of renal transplantation for living-donor kidney transplantation. Except for kidney disease, he had no history of primary liver, heart, or head disease et al. He denied smoking and drinking. Tacrolimus combined with mycophenolate mofetil and prednisolone was applied as anti-rejection regimen. The dose of tacrolimus was adjusted according to the drug serum concentration. At the same time, oral ganciclovir, voriconazole and esomeprazole were used to prevent CMV and fungus infection and esophagogastroduodenal complications. The patient recovered smoothly. Serum creatinine level decreased to 152.0 μmol/L and urine output was normal.

On the 12th week post operation, the patient was admitted to our department because of repeated hematochezia for two weeks, accompanied by dizziness and weakness. No abdominal pain, nausea or vomiting were observed. On physical examination, blood pressure, heart rate and temperature were 95/55 mmHg, 102 beats /minute, 37.5 ℃ respectively. There was mild tenderness at the peri-umbilicus area and the lower right abdomen, without rebound tenderness. Complete blood count revealed a leukocyte count of 7.45 × 109/L, erythrocyte count of 2.05 × 1012/L, hemoglobin level of 57 g/L, platelet count of 241 × 109/L. Mild elevated serum creatinine level of 168.0 umol/L was noted, with a normal BUN level of 6.8 mmol/L. Prothrombin time, apartprothrombin and thrombin time were within normal range. Laboratory indexes about hepatic, cardiac and respiratory function were all normal. Blood and stool cultures for fungus and bacteria showed no growth. Chest CT scan revealed some pulmonary lesions of previous tuberculosis, and serum T-SPOT.TB was negative. There were no abnormal findings in abdominal doppler ultrasound. Esophagogastroduodenoscopy was firstly performed and only mild gastritis was observed, with negative rapid urease test for helicobacter pylori infection. Colonoscopy revealed multiple ulcers in ileocecal valve and distal ileum, with massive fresh blood accumulation. These ulcers were oval and deep, covered with white fur or blood scab, the biggest diameter of which was 2.0 cm (Figure 3A-C). Histopathology revealed chronic inflammation with a large number of lymphocytes infiltration (Figure 2C, D), without signs of fungus and parasites infection. Immunohistochemistry stain for CMV was negative. EBER was also negative by in situ hybridization.

The bleeding lessened and eventually ceased after intravenous somatostatin (1.2 mg/d) and oral thalidomide (100 mg/d) for five days. At the same time, because intestinal multiple ulcers due to immunosuppressors was considered, tacrolimus was firstly withdrawn, and cyclosporine combined with mycophenolate mofetil and prednisolone were administered to the patient. Additionally, the patient was put on oral thalidomide at a dose of 100 mg/d during four weeks. Colonoscopy at fourth week of follow-up revealed remarkable healing of the ulcers with scar tissue in ileocecal valve and distal ileum (Figure 3D-F). There was no recurrent bleeding during one year of follow-up. No organ rejection was found after withdrawing of tacrolimus as well.

**DISCUSSION**

It is well known that patients after solid organ transplantation are particularly at risk for GI complications. Severe GI complications such as GI bleeding and GI perforation may negatively influence long-term outcome, and become deadly. It had been reported that GI bleeding occurred in 2.3%-6.4% patients after liver transplantation[8,9] and GI perforation in 2.9% patients after renal transplantation[7]. Ulcer diseases are important cause of GI bleeding and perforation that can also manifest with symptoms such as abdominal pain or diarrhea. Most of these ulcers locate at anastomotic stoma or gastroduodenum, whereas ulcers at intestine or colon are rare. In the two cases, deep and big size of ulcers all located in ileocecal valve and distal ileum without gastroduodenal lesions. In case 1, there was a longer period of diarrhea and abdominal pain, while case 2 mainly presented with acute and massive GI bleeding.

# Differentiation of ulcer diseases in post-transplantation patients is always difficult. Common and uncommon pathogenesis such as helicobacter pylori infection, ischemia, infection of CMV, EBV, mycobacteria and fungus, post-transplant lymphoproliferative disorders (PTLDs) should be considered. In the present two cases, as ulcers were in ileocecal valve and distal ileum, helicobacter pylori infection was not regarded as pathogen. Clinical manifestation and the endoscopic characteristics of ulcers did not support the pathogenesis of ischemia. Because of negative founding in chest CT scan, serum T-SPOT.TB and histopathology of ulcers, mycobacteria and fungus infection were also excluded. CMV infection is common in patients with solid organ transplantation and attention should be paid in case of gastrointestinal ulcers. A study of renal transplant patients susceptible to a variety of GI complications such as infections, ulcer disease, and malignancies revealed that CMV infection occurred in 11% of all patients[1]. Although oral ganciclovir preventive strategy was used in case two, it might be inefficient in some patients and atypical symptoms might be presented[10,11]. Decreased leukocyte count and interstitial pneumonitis were always found in CMV infection, but in both cases, no positive signs about CMV infection were noted in leukocyte count and chest CT scan. More important, immunohistochemistry stain for CMV of ulcer biopsy tissue was negative and both two patients recovered without further anti-CMV therapy. So CMV infection was not considered in these two cases.

# PTLD was most difficult to be excluded in both patients. Especially in case one, the ulcers in ileocecal valve and distal ileum appeared more deep and large, with proliferative tissue around. PTLD is a severe complication after organ transplantation with a cumulative incidence of 1.1% at 18 mo and 4.7% at 15 years and always associated with EBV infection[12]. Lymph nodes, gastrointestinal tract and graft liver were the commonest sites of involvement[13]. The involvement of GI could result in deadly perforation and hemorrhage. In both patients, there was no persistent fever, palpable superficial lymph nodes, enlarged liver or lymph nodes found through chest and abdominal CT scan or ultrasound; EBER was negative by in situ hybridization. Pathology was also not consistent with the characteristics of PTLD. Furthermore, PTLD usually deteriorates fast and is difficult to be treated. But the present two patients gained a stable condition within 1-2 wk, and the ulcers healed rapidly in 4-6 wk. All the evidences didn’t support the diagnosis of PTLD.

# At last, we considered the fact that the development of the ulcers might be correlated with the immunosuppressant itself. Current studies revealed that some immunosuppressants such as mammalian target of rapamycin (mTOR) inhibitors had inhibitory effects on wound healing. Sirolimus is the most common drug that can lead to the impairment of wound healing and the most common wound complication is skin or dermal eruption[14-17]. Therefore the immunosuppresants was considered to be a possible cause for impairment of GI epithelium. Fortunately, both patients recovered fast after stopping sirolimus and tacrolimus, supporting our speculation. In [Smith AD](http://www.ncbi.nlm.nih.gov/pubmed/?term=Smith%20AD%5BAuthor%5D&cauthor=true&cauthor_uid=15740563) ’s report, three liver transplant patients taking sirolimus suffered from gastrointestinal hemorrhage due to complicated gastroduodenal ulcer. The ulcers in two patients healed only after discontinuation of sirolimus, and the third patient died of massive gastrointestinal bleeding[6].

Thalidomide has anti-angiogenic properties and seems effective in some cases of GI bleeding especially angiodysplasia-related bleeding[18-20]. It is also used in some inflammatory and ulcerative diseases like inflammatory bowel disease, some skin and oral ulcers, because of its anti-inflammatory and immunomodulatory effects[20-22]. In our clinical practice***,*** thalidomide is effective in some unexplained and refractory multiple ulcers of intestine and related GI bleeding. It also seemed to work in our present two patients. Thalidomide was administrated at a dose of 100 mg/d for two weeks and four weeks respectively, and no severe side effects were found.

In summary, some types of immunosuppressants such as sirolimus and tacrolimus can lead to impairment of GI track and sometimes severe ulcers would occur. Withdrawing them or switching to other immunosuppressants might be effective.

**COMMENTS**

***Case characteristics***

A 56-year-old man presented with severe diarrhea and abdominal pain after orthotopic liver transplantation, and a 34-year-old man presented with hematochezia and severe anemia after living-donor kidney transplantation.

***Clinical diagnosis***

Multiple giant ulcers in distal ileum and ileocecal valve caused by immunosuppressants

***Differential diagnosis***

Common and uncommon pathogenesis of gastrointestinal (GI) ulcers in solid organ transplant recipient such as helicobacter pylori infection, ischemia, infection of cytomegalovirus (CMV), Epstein–Barr virus (EBV), mycobacteria and fungus, Post-transplant lymphoproliferative disorders (PTLDs) should be considered.

***Laboratory diagnosis***

Blood and stool cultures for fungus and bacteria showed no growth, and serum T-SPOT.TB was negative.

***Imaging diagnosis***

CT scan revealed no current tuberculosis, and there were no abnormal findings in abdominal enhanced CT or doppler ultrasound.

***Endoscopic diagnosis***

Colonoscopy revealed multiple giant and deep ulcers in ileocecal valve and distal ileum.

***Pathological diagnosis***

Histopathology revealed chronic inflammation without signs of fungus and parasites infection, negative immunohistochemistry stain for CMV, and negative stain for EBER by in situ hybridization.

***Treatment***

Sirolimus or tacrolimus was withdrawed and thalidomide was administrated.

***Related reports***

Most of GI ulcers locate at anastomotic stoma or gastroduodenum in post-transplant recipient, and ulcers at intestine or colon are rare. Besides ischemia and infection of CMV, EBV, mycobacteria and fungus, use of immunosuppressant might contribute to the impairment of gastrointestinal tract.

***Term explanation***

Post-transplant lymphoproliferative disorders (PTLDs) is the severe complication of solid organ and hematopoietic stem cell transplantation, including lymphoproliferative entities varying from reactive hyperplasia to malignant lymphoma. EBV is the main pathogen of PTLD.

***Experiences and lessons***

In some post-transplantation cases with ileal ulcers, sirolimus or tacrolimus should be considered as a risk factor, and withdrawing them or switching to other immunosuppressants might be effective.

***Peer-review***

This article is very interesting for persons involved in the field of liver and kidney transplantation. The ulcers in distal ileum in solid organ transplant recipients are very rare. So, every experience about management of these patients is very useful.

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**Figure 1 Colonoscopic images of case one.** A-C: Multiple giant and deep ulcers in ileocecal valve and distal ileum, with polypoid hyperplasia; D-F: Rapid healing of the ulcers in ileocecal valve and distal ileum and only two healing 2 stage ulcers left.

**Figure 2 Photomicrograph of biopsy specimens.** A, B: Biopsy specimens of ulcers from case one; C, D: Biopsy specimens of ulcers from case two. Hematoxylin-eosin staining, magnification × 200.

**Figure 3 Multiple ulcers in ileocecal valve and distal ileum, with massive fresh blood accumulation (A-C); Rapid healing of the ulcers with scar tissue in ileocecal valve and distal ileum (D-F).**