Case Report

**De novo** Isolated Gastrointestinal Tract Vasculitis without Associated Systemic Disease in Renal Transplant Recipients Successfully Treated with Rituximab

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**ABSTRACT.** Systemic vasculitic diseases can show recurrence after kidney transplantation, but *de novo* systemic vasculitis is rarely seen after kidney transplantation, and in literature, there are only a few cases. In general population, the incidence of isolated organ vasculitis is unknown, and according to the best of our knowledge, there is no information about *de novo* isolated organ vasculitis after renal transplantation. We report, most probably, the first case of a 40-year-old woman who was restarted on dialysis treatment after renal transplantation and developed isolated gastrointestinal vasculitis and intestinal hemorrhage under immunosuppressive treatment. She was treated successfully with rituximab.

**Introduction**

There are many causes of gastrointestinal (GI) bleeding, and 95% of these patients have easily found lesions, but 5% of the patients may have diagnostic problems.¹ GI tract vasculitis is rarely seen, and it is very important to diagnose GI tract vasculitis to provide treatment immediately to avoid irreversible end-organ damage. In case of delayed diagnosis, mortal complications can be seen like ischemia or perforation of visceral organs. Herein, we report the case of a 40-year-old female patient who needed dialysis after renal transplantation and had isolated GI tract vasculitis and hemorrhage under immunosuppressive treatment who was successfully treated with rituximab.

**Case Report**

Informed consent was obtained from the patient before reporting the case.

A 40-year-old female patient, at 2001 March during her pregnancy, had proteinuria and hypertension and was diagnosed as a chronic renal disease due to hypertension. In August 2011, she had renal transplantation from living donor (her husband). After transplantation, renal functions were normal. In May 2017, due to progressive renal dysfunction and protei-
nuria, she had graft biopsy which was reported as humoral rejection and no sign of vasculitis. She was treated with intravenous immunoglobulin, but graft functions progressively worsened, and in April 2018, she was restarted on hemodialysis treatment three days/week.

In June 2018, she was admitted to hospital with nausea, vomiting, and diarrhea of a two-month duration. On admission, her vital signs were stable, she had pallor, abdomen examination was normal, permanent central catheter for dialysis was present, and she had no residual urine. She was receiving tacrolimus (5 mg/day), azathioprine (100 mg/day), methylprednisolone (5 mg/day), nifedipine (60 mg/day), doxazosin (4 mg/day), and carvedilol 25 mg twice a day. She had no history of using nonsteroidal anti-inflammatory drug or acetylsalicylic acid. Laboratory evaluation showed that her hemoglobin level was 6.1 g/dL, white blood cell level was 9.1 $10^3/μL$, platelet level was 127 $10^3/μL$, erythrocyte sedimentation rate was 54 mm/h (0–20), C-reactive protein was 31 mg/L (0–5), liver and thyroid function tests were normal, hepatitis B, C and HIV serology were negative, and vitamin B12, folic acid, and ferritin levels were also normal. In other hematology parameters such as reticulocyte index, haptoglobin, and direct Coombs, no pathologic finding was present. Rose bengal, Gruber-Widal test, antigliadin antibody, anti-endomysium antibody, and parvovirus B19 DNA PCR were all negative. Quantiferon test, cytomegalovirus (CMV) DNA real-polymerase chain reaction (PCR), and tuberculosis (TB) PCR were also negative.

Fecal microscopy showed that there were no parasites, cyst, or leukocytes and culture was also negative. Clostridium difficile toxin A/B was negative.

After detection of anemia and occult blood positivity of stool, upper GI system endoscopy was performed. At the third part of the duodenum, one large ulcer, which was narrowing the lumen for approximately 1 cm and distally to this, a second smaller ulcer was detected. Biopsy was performed from lateral parts of ulcers and from the middle of ulcers for CMV PCR test. Biopsy showed chronic active inflammation, and CMV was reported negative. Double doses of proton-pump inhibitor treatment were started, but she had 2–3 g/dL hemoglobin decrease per week, and occult blood continued to be positive. Colonoscopy was performed to look for any additional lower GI etiology but did not show any pathologic findings. Therefore, to examine the intestinal segments, double-balloon enteroscopy was performed and 50 cm distal from pylorus was evaluated. There were 2 cm to 4–5 cm sized cavitary ulcers at 6–7 different regions beginning from the third part of the duodenum, covered by necrotic material and narrowing the lumen. The mucosa of the duodenum and jejunum located between the ulcers was normal (Figure 1). Biopsy was taken from lateral and basal parts of duodenal ulcers which showed erosive findings on the small intestinal mucosal epithelium, bleeding under this area, lymphangiectasis, edema at the lamina propria, leukocytic cell infiltration formed by mostly lymphoplasmocytes, and rarely polymorphonuclear cells. In addition, fibrinoid necrosis at vessel walls and fibrin thrombus at lumens of small vessels in the lamina propria were also reported. Besides the mucosal degeneration, vascular damage and fibrinoid necrosis at vessel walls denoting vasculitis were detected. No findings of acute

Figure 1. On endoscopy, multiple, large, cavitating ulcers were seen at the distal part of the duodenum and proximal site of the jejunum.
and chronic graft versus host reaction in crypts and glands were found. Furthermore, tests for infectious causes such as CMV and TB were negative.

The patient was evaluated for autoimmune disorders such as systemic lupus erythematosus (SLE), microscopic polyangiitis, or ischemic causes. Antinuclear antibody, anti-double-stranded DNA, antineutrophil cytoplasmic antibody (p-c), and cryoglobulin were negative. Complement levels were normal. Thoracoabdominal computed tomography and magnetic resonance enterography showed that there were subcentimetric lymph nodes in the mediastinum, mesenteric, and para-aortic areas. Proximal jejunal wall thickness was increased, and submucosal edema was reported. Arterial and venous vascular structures were normal. Considering the diagnosis of small-vessel vasculitis despite having immunosuppressive treatment, rituximab 1000 mg twice given 15 days apart was the choice of treatment instead of cyclophosphamide. One month later, ulcers had totally recovered at endoscopic examination (Figure 2). Hemoglobin levels also remained stable.

Discussion

Vasculitis of the GI tract is rarely seen, but identification by a pathologist is critical for the prevention of end-organ damage. The most common GI tract vasculitic pathologies are immune complex-mediated (SLE, IgA vasculitis, rarely mixed connective tissue disease, and rheumatoid arthritis) and drug-related vasculitis.\textsuperscript{2,3} But also isolated organ vasculitis can be seen as it was reported in a recently published case series.\textsuperscript{4} Furthermore, some systemic disorders such as polyarteritis nodosa and microscopic polyangiitis can be related with GI vasculitis.\textsuperscript{5} Our patient had no sign of physical or serologic findings of any systemic rheumatologic disorder which could involve the GI tract. In addition, despite the strong association of Behçet’s disease with GI system involvement,\textsuperscript{5} there were no physical examination findings of Behçet’s disease including oral aphthosis in our patient.

Mycophenolic acid and mammalian target of rapamycin (mTOR) inhibitors (sirolimus and everolimus) used commonly in renal transplantation are related to GI tract side effects. Common side effects of mTOR inhibitors are diarrhea, abdominal pain, and impaired healing due to antiproliferative effect.\textsuperscript{6} In addition, ulcers in the oral cavity are described, and colon perforation as a result of leukocytic vasculitis developing due to sirolimus treatment after renal transplantation is reported.\textsuperscript{7} Our patient did not take mTOR inhibitor and mycophenolic acid; other medications that she received were not related to vasculitis.

In many transplantation patients who have immunosuppressive treatment, the development and progression of vasculitis is reported.\textsuperscript{8,9} In most of the cases, this is based on an recurrent autoimmune process or infection.\textsuperscript{10} Schriner et al reported a successfully treated patient with increasing the steroid dose who had de novo systemic vasculitis two years after renal transplantation.\textsuperscript{11} Bedani et al reported a case with mortal vasculitis including lungs, pancreas, and GI tract 11 months after renal transplantation.\textsuperscript{12} By Chapel Hill consensus, isolated GI tract vasculitis is classified as single-organ vasculitis described as limited to a single-organ arterial or vessel vasculitis without any proof of systemic vasculitis.\textsuperscript{13} The true incidence
of single-organ vasculitis is unclear, due to some patients later develop evidence of systemic vasculitis.\(^1^4\)

In literature, we were not able to find any information about \textit{de novo} isolated GI tract vasculitis among renal transplanted patients. Our case is probably the first case of isolated small-vessel vasculitis with GI involvement after seven years of renal transplantation. Ischemic reasons that can cause GI ulcers, TB, and other infectious, inflammatory diseases were ruled out. No sign of systemic vasculitis was detected in other organs. Our patient who was already having immunosuppressive treatment dramatically responded to rituximab.

In conclusion, \textit{de novo} isolated GI vasculitis can be rarely seen while on immunosuppressive treatment, and it is difficult to diagnose. For GI ulcers whose etiology cannot be explained in solid organ transplantation patients, vasculitis should be considered in the differential diagnosis.

\textbf{Ethical approval}

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

\textbf{Conflict of interest:} None declared.

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