Case Report (Olgu Sunumu)

Tacrolimus-Associated Thrombotic Microangiopathy Presenting with Ischemic Colitis After Kidney Transplantation: A Case Report

Böbrek Nakli Sonrası İskemik Kolit ile Prezente olan Tacrolimus İlişkili Trombotik Mikroanjiyopati: Bir Olgu Sunumu

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Özet

Kalsinörin inhibitörleri (KNİ), böbrek transplantasyonu sonrası immünosupresif rejimin önemli bir üyesidir. KNİ'ler bazı sitokinlerin gen transkripsiyonunu inhibe ederek, T hücre aktivasyonunu baskılar. Böbrek transplantasyonu yapılan hastaların çoğunda takrolimus tercih edilmektedir. Trombotik mikroanjiyopati (TMA), KNİ tedavisinin ciddi fakat nadir görülen bir komplikasyonudur. TMA, mikrovasküler tromboza yol açan arteriyollerin ve kapillerlerin spesifik bir patolojik lezyonunu tanımlar. Olgumuz, 45 yaşında erkek hasta olup otozomal dominant polikistik böbrek hastalığı (ODPKBH) nedeniyle beş ay önce böbrek transplantasyonu olmuştur. İdame immünosüpresif tedavisi takrolimus içermektedir. Nakil sonrası beşinci ayda karın ağrısı ve kanlı ishal şikayeti oluşmuş. Yapılan kolonoskopide çıkan kolonun mukozası ödematöz ve eritematöz olarak saptandı. Biyopsi örneklerinin incelemesinde lamina propriyadaki damar lümeni içindeki mikrotrombüs odakları gösterildi. Abdominal bilgisayarlı tomografi (BT) anjiyografi ile vasküler tromboz veya tıkanıklık araştırılıp dışlanmıştır. Bakılan periferik yaymada, şistositler ve ılımlı derecede trombositopeni izlenildi. Klinik, laboratuvar ve histolojik bulgular ışığında TMA tanısı konuldu. Takrolimus patolojik sürecin tetikleyicisi olarak değerlendirildi, hızlıca everolimus ile değiştirildi. Daha sonra laboratuvar anormallikleri ve klinik semptomlar düzeldi. Biz bu olgu sunumunda; ilaca bağlı TMA ve kolonun mikrovasküler gibi atipik tutulum lokalizasyonuna dikkat çekmeyi amaçladık.

Anahtar kelimeler: Böbrek nakli, İskemik kolit, Takrolimus, Trombotik mikroanjiyopati

Abstract

Calcineurin inhibitors (CNIs) are a significant component of the immunosuppressive regimen after kidney transplantation. By inhibiting cytokine gene transcription, CNIs suppress T cell and T cell-dependent B cell activation. Tacrolimus is preferred in most patients undergoing kidney transplantation. Thrombotic microangiopathy (TMA) is a severe but rare complication of CNIs therapy. TMA defines a specific pathologic lesion of arterioles and capillaries that leads to microvascular thrombosis. A 45-year-old male underwent kidney transplantation five months ago due to autosomal dominant polycystic kidney disease (ADPKD). His triple-maintenance immunosuppressive therapy includes tacrolimus. Abdominal pain and bloody diarrhea occurred in the fifth month of posttransplant. The edematous and erythematous mucosa of the ascending colon was detected on the colonoscopy. The foci of microthrombi inside the vessel lumen in the lamina propria were shown biopsy. The thrombosis or occlusion was excluded with computerized tomography (CT) angiography in abdominal vessels. The fragmented red blood cells and moderate thrombocytopenia were detected on the peripheral blood smear. Eventually, TMA diagnosis was established through laboratory and histological findings. Tacrolimus was suspected as the trigger of the pathological process and promptly switched to the everolimus. Afterward, laboratory abnormalities and clinical symptoms were improved. In this case, we intend to emphasize drug-associated TMA and atypical presentations, such as colonic microvasculature involvement.

Keywords: Kidney transplantation, Tacrolimus, Thrombotic microangiopathy, Ischemic colitis

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INTRODUCTION

Calcineurin inhibitors (CNIs) are a significant component of the immunosuppressive regimen after kidney transplantation. CNIs affect via reducing the transcription of interleukin (IL)-2 and several cytokines in T lymphocytes. Despite being chemically irrelevant, tacrolimus and cyclosporine exert similar biological effects in cells (1). In most patients undergoing kidney transplantation, tacrolimus is preferred because it is associated with reduced acute rejection rates and similar overall costs (2).

Thrombotic microangiopathy (TMA) is a rare but serious adverse effect of CNIs. TMA defines a specific pathologic lesion of arterioles and capillaries that leads to microvascular thrombosis. TMA is diagnosed by tissue biopsy (3). However, it is generally inferred from the clues of microangiopathic hemolytic anemia (MAHA) or thrombocytopenia. MAHA is a descriptive term for non-immune hemolysis resulting from the splitting of erythrocytes in the vascular lumen. Schistocytes are significant evidence of red cell fragmentation in MAHA.

Occasionally, TMA may present without systemic MAHA or thrombocytopenia, and clinical presentation is limited to the organ, such as the kidney (4). In this case, we report a tacrolimus-associated TMA clinically manifested via only colonic microvasculature injury.

CASE REPORT

A 45-year-old male underwent kidney transplantation due to autosomal dominant polycystic kidney disease (ADPKD). The posttransplant immunosuppressive regimen consisted of tacrolimus, mycophenolate mofetil, and prednisolone. Five months after transplantation, he applied to the emergency department due to abdominal pain and bloody diarrhea lasting for three days. He was hospitalized due to volume depletion and minimal kidney function deterioration.

The vital signs were stable, and abdominal tenderness with increased bowel movements was detected on the physical examination. The count of defecation was ten times a day, runny and bloody. The initial laboratory results were as follows; blood urea nitrogen (BUN): 40 mg/dl, creatinine: 1,4 mg/dl, albumin: 3,8 g/dl, alanine transaminase (ALT): 26 IU/L, aspartate aminotransferase (AST): 75 IU/L, lactate dehydrogenase (LDH): 733 IU/L, bilirubin: 1,0 mg/dl, CRP: 34 mg/L, leukocyte: 3.2 10^3/µl, hemoglobin: 10.2 g/dl, platelet: 92 10^3/µl, prothrombin time (PT): 12 seconds, activated partial thromboplastin time (aPTT): 28 seconds, and tacrolimus through level: 8.3 ng/ml (on target level).

The impaired kidney function was primarily considered prerenal azotemia, so an allograft biopsy was not performed. Creatinine level decreased to baseline (1.2 mg/dl) afterward with parenteral saline hydration. Also, a remarkable alteration was not revealed in urinalyses, such as proteinuria and hematuria. However, bloody diarrhea persisted despite the empiric antibiotic therapy. Any pathogen was not isolated in stool cultures and microscopic examination. Clostridium toxin A-B tests resulted in a negative. Furthermore, polymerase chain reaction (PCR) based cytomegalovirus (CMV) detection resulted in negative blood and stool samples.

The ascending colon mucosa was edematous and erythematous; also, aphthous lesions were observed in the sigmoidal and transverse colon segments in the colonoscopic examination. The biopsy samples were obtained, and colonoscopic views are shown in **Figure 1**.

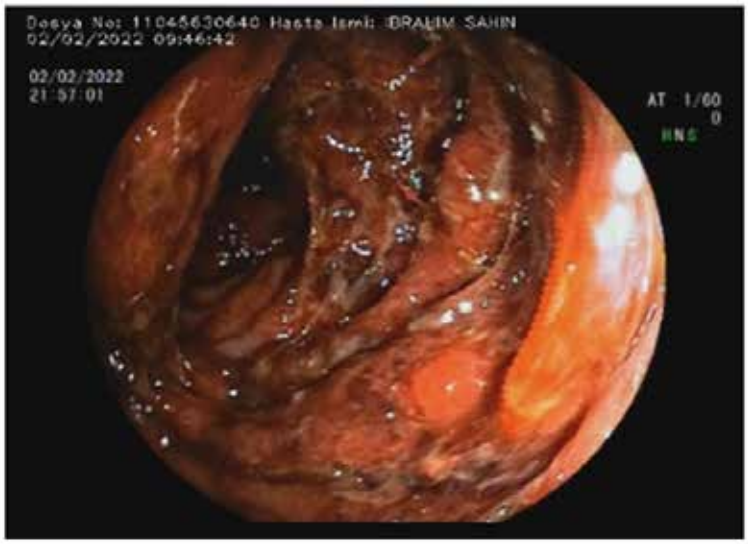

Figure 1. Colonoscopic image. Edematous and erythematous bowel mucosa on colonoscopy.

A colon biopsy was reported as ischemic colitis, and the section is shown in **Figure 2**. In the pathological examination, foci of microthrombi inside the vessel lumen in the lamina propria and regenerative findings accompanying ischemic changes were observed on the light microscopy. Also, swollen endothelial cells were observed. The samples were not stained with IgA, IgG, and CMV antigens on immunohistochemical detection.

Subsequently, an occlusion or thrombosis of vessels was not observed in computerized abdominal tomography (CT) angiography imaging, and only segmental bowel wall thickening was demonstrated (image is shown in **Figure 3**). The cardiac-originated thromboembolism was excluded via echocardiography and electrocardiography.

The peripheral blood smear was evaluated for moderate thrombocytopenia. The fragmented red blood cells (schistocytes) were detected and shown in **Figure 4**. However, remarkable findings of MAHA were not determined, such as decreased haptoglobin and reticulocytosis. ADAMTS13 (A disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13) activity level, and complement levels (C3 and C4) were in the normal range. The Coombs tests were negative.

Eventually, we established the tissue-limited TMA diagnosis in this case through histological and laboratory clues. CNI was suspected as the trigger of the pathological process. Tacrolimus was promptly switched to the everolimus. Also, anticoagulant therapy was continued for microthrombosis. However, therapeutic plasma exchange (TPE) or complement-targeted therapeutic was not initially administered. The patient was discharged after the complaints were relieved. Elevated LDH levels, schistocytes, and thrombocytopenia resolved in the outpatient follow-up over time. Lastly, bowel injury has been regressed in consecutive radiological examinations.

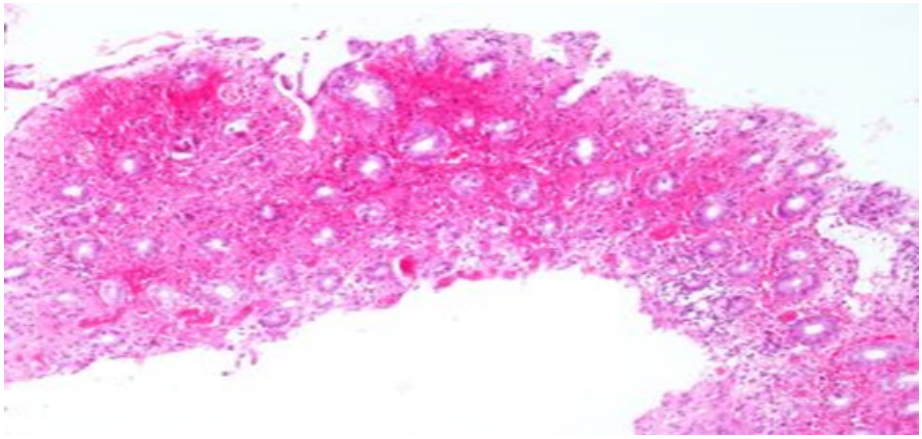

Figure 2. Pathology specimen. Light microscopy showing vanishing crypt, hemorrhage in lamina propia and microthombi in capilleries; consistent with ischemic colitis. The endothelial cells was swollen. (200x, H&E stain)

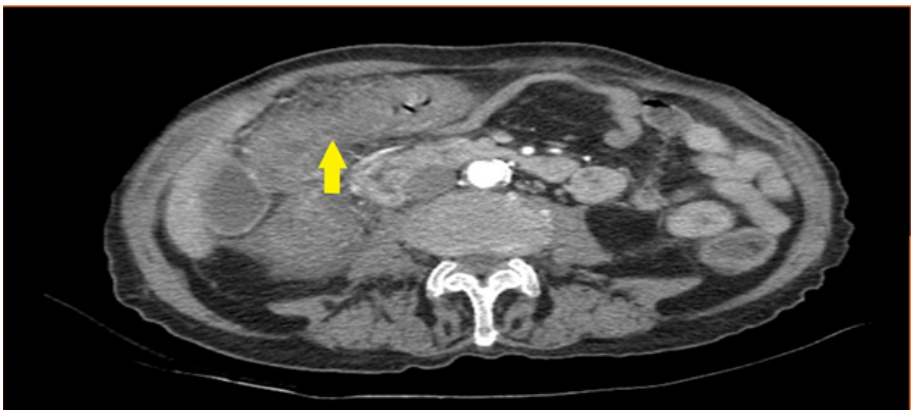

Figure 3. Abdominal computed tomography. The colitis in the transerve colon, arrow shows the thickening bowel wall.

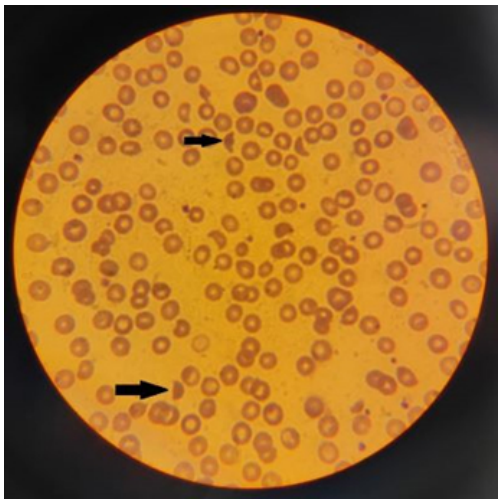

Figure 4. High-power view of a peripheral blood smear. Multiple schistocyte *(arrows)* and the platelet number is reduced.

DISCUSSION

We have presented a case of colon-limited injurious TMA attack, which is triggered by tacrolimus. This conclusion is based on several clinical and laboratory assessments. This mentioned case was rather complicated and involved multiple scenarios that could possibly explain the clinic. Initially, the lack of vascular occlusions in imaging led to differential diagnosis. Subsequently, the diagnosis of TMA was established with biopsy-proven ischemic colitis, moderate thrombocytopenia, and fragmented red blood cells. The primary TMAs excluded, and then secondary causes of TMA were evaluated. Normal ADAMTS13 activity and complement levels were essential for exclusion. The infectious causes were excluded regarding bloody diarrhea and hemolytic uremic syndrome (HUS), including Enterohemorrhagic Escherichia coli (EHEC), Shigella dysenteriae, and CMV. Indeed, various causes and factors are listed in the pathogenesis of secondary TMA. However, the tacrolimus with TMA relationship is well known and has been reported many times in the literature. Therefore, our first manipulation was that the drug withdrawal due to TMA was attributed to tacrolimus. As a result, the clinical course has been alleviated by treatment cessation. The diagnostic approach can be summarized with this algorithm.

TMA is a severe occlusive microvascular disease characterized by aggregation of platelets, thrombocytopenia, and erythrocyte mechanical injury. TMA is manifested as fragmentation of erythrocytes in blood smear and increased LDH levels. Pathologically, there is an aggregation of platelets with microthrombi in arterioles. Moreover, histological findings involve diffuse and global endothelial swelling, double contours of the glomerular basement membranes, and scattered foamy macrophages. Occlusion of microcirculation leads to ischemic injury to affected organs (5). Kidneys are an essential affected organ in TMA, and it is almost manifested as acute kidney injury. Endothelial cell activation and alteration are at the center of pathogenesis. The various factors listed in the trigger of TMA; such as thrombotic thrombocytopenic purpura, bacterial toxins, uncontrolled complement activation, malignancy, and drugs (6).

Various atypical manifestations of TMA have been reported, such as pancreatitis, hepatitis, mesenteric ischemia, acute respiratory distress syndrome, and ischemic retinopathy (7,8). Ischemic colitis as a manifestation of TMA was first reported in 1989 and also has been reported many times since then (9,10).

Intestinal ischemia is a consequence of reducing intestinal blood flow and affecting the small or large intestine. The arterial occlusion (embolic, thrombotic), venous thrombosis, or hypoperfusion of the mesenteric vasculature can be causative. Most cases of colonic ischemia are frequently transient and improve without sequelae (11). The manifestations of acute colonic ischemia can range from mild to severe. Moderate rectal bleeding or bloody diarrhea usually occurs within 24 hours of the onset of abdominal pain. Hematochezia is more commonly a sign of colonic ischemia than small bowel ischemia. Conservative management is often sufficient in most cases (12).

Tacrolimus and cyclosporine selectively inhibit cytosolic calcineurin in cells. This inhibition leads to a block in the translocation of the cytosolic component of the nuclear factor of activated T cells (NF-AT). Thereby, the transcription of interleukin (IL)-2 and several cytokines decrease in T lymphocytes (1). CNIs have been the mainstay of immunosuppression in kidney transplantation.

In clinical practice, monitoring and dose adjustments of CNIs are essential. Also, distinct target levels are suggested in various clinical conditions. Tacrolimus achieves steady-state concentrations after four to six doses (13). Nephrotoxicity, hypertension, neurotoxicity, glucose intolerance, electrolyte disturbances, increased risk of malignancy, and gastrointestinal complaints are significant side effects of CNIs.

TMA is a well-known and rare complication of CNIs. CNIs cause non-immune, dose-dependent endothelial dysfunction and increased platelet aggregation, possibly by inhibiting prostacyclins (14). Also, de novo TMA induced by CNIs after kidney transplantation has been reported many times. This mentioned circumstance can present tissue-restricted or systemic.

Management of CNIs-associated TMA involves only discontinuation of the drug and supportive care. The alteration of CNIs with mammalian target of rapamycin inhibitors (mTOR) has been reported to be a good choice (6). In the reported series, after the discontinuation of tacrolimus, LDH was the first parameter to respond dramatically followed by the disappearance of the fragmented red cells, and the reversal of thrombocytopenia (15).

Drug-induced thrombotic microangiopathy (DITMA) diagnosis is established clinically, and there is no specific diagnostic test. Furthermore, a tissue biopsy may exhibit evidence of a TMA but is not required to make a presumptive diagnosis. Also, pathological interpretation can not recognize DITMA from other reasons for TMA. TPE is controversial in the management of DITMA. There is a lack of high-quality proof for the utility of TPE in DITMA.

The administration of PTE was not preferred for this due to its pathophysiological mechanism. Nevertheless, a sufficient response was attained via this approach. The presence of adequate ADAMTS13 activity supported the decision. The complement-targeted therapeutic could be considered if we encounter refractory TMA despite drug cessation.

In conclusion, early diagnosis of secondary TMAs has clinical significance for the reversal of organ damage. Also, elucidation of the etiology requires comprehensive investigation in secondary TMAs. Kidney transplantation recipients have exhibited various atypical clinical manifestations due to immunocompromising status and multi-drug medication. In this case, we have presented an unexpected location for tissue-limited TMA accompanied by mild laboratory abnormalities. Eventually, we intend to emphasize the crucial complication of tacrolimus in transplantation practice.

REFERENCES

1. Azzi JR, Sayegh MH, Mallat SG. Calcineurin inhibitors: 40 years later, can't live without. The Journal of Immunology 2013; 191(12):5785-91.
2. Webster AC, Woodroffe RC, Taylor RS, Chapman JR, Craig JC. Tacrolimus versus ciclosporin as primary immunosuppression for kidney transplant recipients: meta-analysis and meta-regression of randomised trial data. BMJ 2005; 331(7520):810.
3. George JN, Nester CM. Syndromes of Thrombotic Microangiopathy. New England Journal of Medicine 2014; 371(7):654-66.
4. Toriu N, Sekine A, Mizuno H, Hasegawa E, Yamanouchi M, Hiramatsu R, et al. Renal-limited thrombotic microangiopathy due to bevacizumab therapy for metastatic colorectal cancer: a case report. Case Reports in Oncology 2019; 12(2):391-400.
5. Brocklebank V, Wood KM, Kavanagh D. Thrombotic microangiopathy and the kidney. Clinical Journal of the American Society of Nephrology 2018; 13(2):300-17.
6. Riedl M, Fakhouri F, Le Quintrec M, Noone DG, Jungraithmayr TC, Fremeaux-Bacchi V, et al. Spectrum of complement-mediated thrombotic microangiopathies: pathogenetic insights identifying novel treatment approaches. Seminars in Thrombosis and Hemostasis 2014; 40(4):444-64.
7. Kathula SK, Koduri J, Mall S, Chang JC. A case report of total abdominal hysterectomy resulting in acute thrombotic thrombocytopenic purpura with pancreatitis and hepatitis: complete resolution with plasma exchange therapy. Therapeutic Apheresis and Dialysis 2003; 7(3):373-4.
8. Smirnova T, Kozlovskaya N, Sheludchenko V. Ocular manifestations of primary thrombotic microangiopathy. Vestnik Oftalmologii 2021; 137(5):138-44.
9. Dubois A, Lyonnet P, Cohendy R, Said HO, Branger B, Raffanel C, et al. Ischemic colitis as a manifestation of Moschkowitz's syndrome. In: Annales de Gastroenterologie et d'Hepatologie: 1989; 1989: 19.
10. See JR, Sabagh T, Barde CJ. Thrombotic thrombocytopenic purpura: a case presenting with acute ischemic colitis. Case Reports in Hematology 2013; 2013:592930.
11. Oglat A, Quigley EM. Colonic ischemia: usual and unusual presentations and their management. Current Opinion in Gastroenterology 2017; 33(1):34-40.
12. Tadros M, Majumder S, Birk JW. A review of ischemic colitis: is our clinical recognition and management adequate? Expert Review of Gastroenterology & Hepatology 2013; 7(7):605-13.
13. Staatz CE, Tett SE. Clinical pharmacokinetics and pharmacodynamics of tacrolimus in solid organ transplantation. Clinical Pharmacokinetics 2004; 43(10):623-53.
14. Chatzikonstantinou T, Gavriilaki M, Anagnostopoulos A, Gavriilaki E. An update in drug-induced thrombotic microangiopathy. Frontiers in Medicine 2020; 7:212.
15. Nwaba A, MacQuillan G, Adams LA, Garas G, Delriviere L, Augustson B, et al. Tacrolimus-induced thrombotic microangiopathy in orthotopic liver transplant patients: case series of four patients. Internal Medicine Journal 2013; 43(3):328-33.