LETTER TO THE EDITOR

Colonic perforation associated with leukocytoclastic vasculitis caused by Sirolimus toxicity following renal transplantation

doi:10.1111/j.1432-2277.2006.00276.x

Target of Rapamycin (TOR) inhibitors have been introduced in clinical transplantation during the past decade. Common side effects of TOR inhibitors include diarrhea and abdominal discomfort, acne, pancytopenia and wound healing disturbances because of the antiproliferative effects [1,2]. Furthermore, ulcers within the oral cavity have been described.

A 35-year-old male patient with phosphoribosyl transferase inhibitor deficiency underwent his fourth kidney transplantation after three failures because of recurrent disease. At this time the patient had developed 66% preformed antibodies, however, the crossmatch was negative. Initial immunosuppression consisted of Tacrolimus, Sirolimus (SIR) and steroids. One week later, the patient developed acute vascular rejection (C4d positive signal on renal biopsy), which was treated with bolused steroids (500 mg of methylprednisolone on three consecutive days) and extensive plasma exchange. This was followed by multiple sessions of immunoapheresis over 6 weeks. Ganciclovir prophylaxis was given for 3 months. Tacrolimus dose was reduced and mycophenolic acid was added and the patient was kept on quadruple drug therapy. The remaining course was uncomplicated; the graft recovered and functioned well. Sixteen-months post-transplant, the patient developed respiratory tract infection and was prescribed Clarithromycin by his general practitioner. Few days later, he presented with severe abdominal pain, fever and watery diarrhea accompaigned by deterioration of the renal graft function. Colonoscopy showed multiple ulcers at various parts of the colon. Histology revealed unspecific ulcerations – no cause for the lesions could be identified, enteric pathogens such as Salmonella, Clostridium difficile and Rotavirus were excluded [3,4]. Repeated testing for cytomegalie virus (CMV) or Ebstein-Barr-virus (EBV) replication were also negative. Conservative treatment with metronidazol and ciprofloxacin was initiated; C-reactive protein and leukocyte count decreased and the patient's condition and the renal graft function improved. The following day SIR level was measured, which was as high as 25 ng/dl. The agent was immediately withdrawn. After initial improvement, the patient's condition deteriorated again and he finally developed acute abdomen with graft failure. Abdominal X-ray demonstrated massive intraperitoneal air and CT scan identified a thickened colonic wall and sigmoid perforation (Fig. 1). The sigmoid colon was resected and antibiotic therapy was changed to piperacillin/tazobactam (4.5 g q 8 h). After initial improvement, the patient developed sepsis and died because of multiorgan failure. Autopsy showed a steatosed liver, active colitis with multiple ulcers and ulceration at the cardioesophageal junction. Histology of colonic and gastric ulcers revealed atypical inflammatory changes within the wall with signs of vasculitis (Fig. 2). The blood vessels within the mesenterium were infiltrated by fibrin deposits. The histological features were consistent with leukocytoclastic vasculitis (LCV). The ulcerations were suspected to be of ischemic origin because of the vasculitis.

Leukocytoclastic vasculitis is a necrotizing vasculitis with segmental areas of transmural infiltration and disruption of the vessel architecture by neutrophils with fibrinoid necrosis [5]. It is known to be caused by autoimmune diseases, infections and drugs. SIR is absorbed from the upper gastrointestinal tract and 50% of the drug is metabolized in the gut mucosa [6]. As LCV mainly involved mesenteric blood vessels, causing ischemic ulcers within the dependent colonic segments, colonoscopic biopsies could not identify the process. LCV has been described primarily in the skin but many patients present with systemic manifestations involving joints, kidneys and the gastrointestinal tract. SIR associated cutaneous LCV has been reported after kidney–pancreas and lung transplantation and in children [7,8,9]. It is tempting to suspect, that the required intensified immunosuppression in this patient also contributed to the development of LCV. SIR has been shown to be a useful agent in transplantation, however, SIR toxicity must be considered as a possible differential diagnosis in patients presenting with severe abdominal pain and/or gastrointestinal ulcers. Physicians must be educated on the potential drug interaction of SIR and some antimicrobial agents such as macrolides.

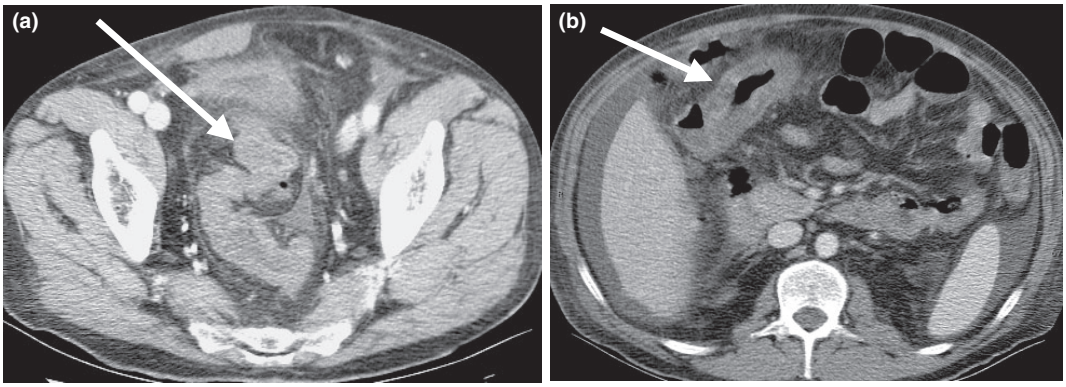

Figure 1 (a) CT scan: thickening of the wall of the sigmoid colon and rectum (arrow). (b) CT scan: thickening of the wall of the ascending colon (arrow), free air and perihepatic fluid collection.

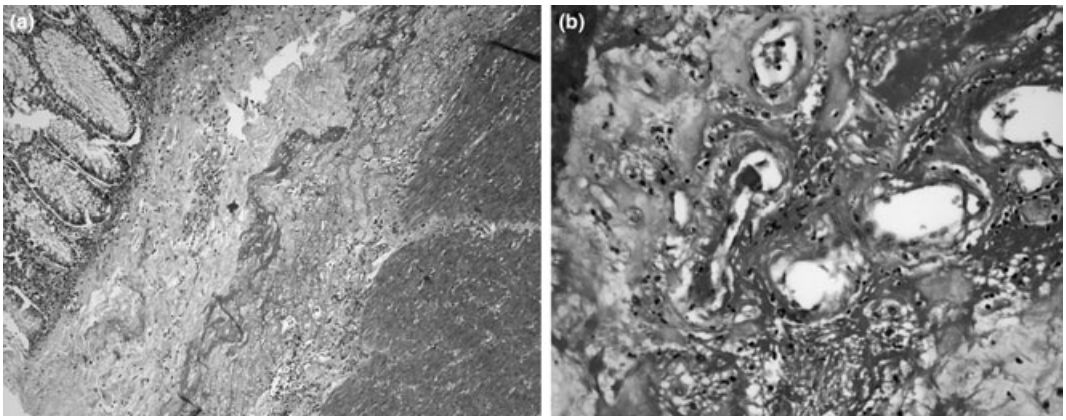

Figure 2 Histology: colonic wall with fibrin deposits within the wall close to vascular structures; magnification: (a) ×100; (b) ×400.

Beate Hugl,[1] Karl Lhotta,[2] Christian Ensinger,[3] Micole Cont,[4] Reinhold Kafka,[4] Raimund Margreiter,[4] Alexander Rosenkranz[2] and Hugo Bonatti[4]

1 Department of Vascular Surgery, Innsbruck University Hospital, Innsbruck, Austria
2 Department of Nephrology, Innsbruck University Hospital, Innsbruck, Austria
3 Institute of Pathology, Innsbruck University Hospital, Innsbruck, Austria
4 Department of General and Transplant Surgery, Innsbruck University Hospital, Innsbruck, Austria

References

1. Sehgal SN. Rapamune (RAPA, rapamycin, sirolismus): mechanism of action immunosuppressive effect results from blockade of signal transduction and inhibition of cell cycle progression. *Clin Biochem* 1998; **31**: 335.
2. Groth CG, Bäckman L, Morlaes JM, *et al.* Sirolismus (rapamycin)-based therapy in human renal transplantation. *Transplantation* 1999; **67**: 1036.
3. Stelzmueller I, Dunst KM, Hengster P, *et al.* A cluster of rotavirus enteritis in adult transplant recipients. *Transpl Int* 2005; **18**: 470.
4. Biebl M, Stelzmüller I, Nachbaur D, Wolf D, Suman G, Bonatti H. Fatal clostridium difficile-associated toxic megacolon following unrelated stem-cell. *Eur Surg Acta Chir Austriaca* 2006; **38**: 1–5.
5. Fiorentino DF. Cutaneous vasculitis. *J Am Acad Dermatol* 2003; **48**: 311.
6. Crowe A, Bruelisauer A, Duerr L, Guntz P, Lemair M. Absorption and intestinal metabolism of SDZ-RAD and rapamycin in rats. *Drug Metab Dispos* 1999; **27**: 627.
7. Hardinger KL, Cornelius LA, Trulock EP, *et al.* Sirolimus-induced leukocytoclastic vasculitis. *Transplantation* 2002; **74**: 739.
8. Pasqualotto AC, Bianco PD, Sukiennik TCT, *et al.* Sirolimus-induced leukocytoclastic vasculitis: the second case report. *Am J Transplant* 2004; **4**: 1549.
9. Nagarajan S, Friedrich T, Garcia M, Kambham N, Sarwal MM. Gastrointestinal leukocytoclastic vasculitis: an adverse effect of sirolimus. *Pediatr Transplant* 2005; **9**: 97.

