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CASE REPORT

# Hemolytic uremic syndrome following Campath-1H induction

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## Summary

Hemolytic uremic syndrome (HUS) is a rare complication following solid organ transplantation. We report on a patient who underwent renal transplantation using Campath-1H induction and tacrolimus maintenance therapy who developed HUS, which was managed by plasma exchange and switch to Rapamycin. However, graft function could not be restored.

## Introduction

Hemolytic uremic syndrome (HUS) associated with Shiga-like toxin producing *Escherichia coli* is one of the most common indications for pediatric renal transplantation [1]. HUS is also a rare complication following adult solid organ transplantation [2]. The exact underlying mechanism of HUS post transplant is not fully understood. Calcineurin inhibitors (CNI) have been linked to the development of HUS; however, some cases are clearly associated with factor H deficiency and therefore it has been attempted to treat this complication by auxiliary liver transplantation [3,4]. Cyclosporine A (CyA) has been described to cause HUS and it was thought that because of the different binding proteins, tacrolimus (TAC) would not cause HUS. In fact, switch from CyA to TAC has been successfully carried out in some cases [5], but both CNIs have been described to be involved [6]. More recently also TAC-associated HUS has been described and it was suggested, besides extensive plasma exchange, to switch immunosuppression from CNIs to Rapamycin [6–8]. Alemtuzumab (Campath-1H) is a humanized anti-CD52 antibody, which has been used as induction therapy following solid organ transplantation [9]. The concept of intensified initial immunosuppression by depletion of the vast majority of immunocompetent cells including T-, B-, and NK cells seems reasonable as long-term immunosuppression can be maintained at a lower level than previously used [10,11]. Thus far, no data are available of HUS in patients treated with alemtuzumab neither as induction for nor as complication after solid organ transplantation. Only a single case of HUS following application of alemtuzumab for therapy of rheumatoid arthritis has been published [12]. We report on a patient who underwent renal transplantation using Campath-1H induction and TAC maintenance therapy, developed HUS during the second month post-transplant, and which presented in an atypical way.

## Case report

A 39-year-old male underwent cadaveric kidney transplantation for chronic glomerulonephritis in September 2004. The pretransplant crossmatch was negative and the patient tested negative for panel reactive antibodies (PRA). He received two boluses of 20 mg of Campath-1H together with 500/250 mg methylprednisolon on days 0 and 1 post-transplant. From day 3 on, he received TAC monotherapy with trough levels of 8–12 ng/ml. Initial graft function was good and the patient experienced no acute rejection. He developed oral Herpes simplex (HSV) infection and fever of unknown origin during the second week, which were both successfully treated with acyclovir and ciprofloxacin, respectively. He was discharged in good condition with a serum creatinine of 1.6 mg/dl on day 12 post-transplant. After another week with stable graft function, the patient was admitted to a local hospital with sudden deterioration of renal function and a rise in serum creatinine reaching 5.2 mg/dl 21 days after kidney transplantation. He then became anuric and was transferred to our center. The patient presented, besides dialysis-dependent renal failure, in a good clinical condition. On ultrasonography, a massive swelling of the graft was found and a missing telediastolic signal (Fig. 1). As lymphocyte count was 0.5% of a total of 9000 cells/ml, cell-mediated rejection seemed unlikely. Hemoglobin on admission was 9.3 mg/dl and platelet count was 175 000/ml. The patient underwent plasma exchange and received bolused steroids (a total of 1250 mg on three consecutive days). A renal biopsy was performed which did not show any evidence for acute rejection but tubular necrosis, interstitial edema and hyalin protein-storage within the tubuli (Fig. 2a). Immunohistochemistry for C4d was negative and there were no signs of a polyoma infection. Hence, toxic tubulopathy was suspected and trimethoprime/sulfamethoxazole was thought to be the causing drug, which therefore was withdrawn. The patient became oliguric and ultrasonography findings improved; however, he still required intermittent hemodialysis. The further course was complicated by watery diarrhea; however, no pathogens were isolated from stool. Screening included *Clostridium difficile*, *Rotavirus*, *Salmonella*, *Shigella*, *E. coli*, *Yersinia*, and *Campylobacter*. Colonoscopy did not reveal any abnormalities and neither CMV nor EBV PCR became positive. During the following week, the patient became progressively thrombopenic and fragmentocytes were detected in the blood. Platelets decreased from 175 000/ml upon admission to <40 000/ml. Atypical presentation of HUS was suspected and a second biopsy was performed which clearly confirmed the diagnosis. Histopathology thereby revealed severe thrombotic microangiopathy of glomeruli and arteries with mediolysis within small arteries (Fig. 2b). The patient consecutively underwent a series of six plasma exchanges and was switched from TAC to sirolimus (trough levels 4–8 ng/dl). Within 1 week, platelets recovered from a nadir of 37 000/ml to >100 000/ml and diuresis increased to >1000 ml/24 h. Except for significant hypertension which was treated by continuous infusion of nifedipin and urapidil in combination with betablockers, no complications were observed. Following further clinical improvement, another

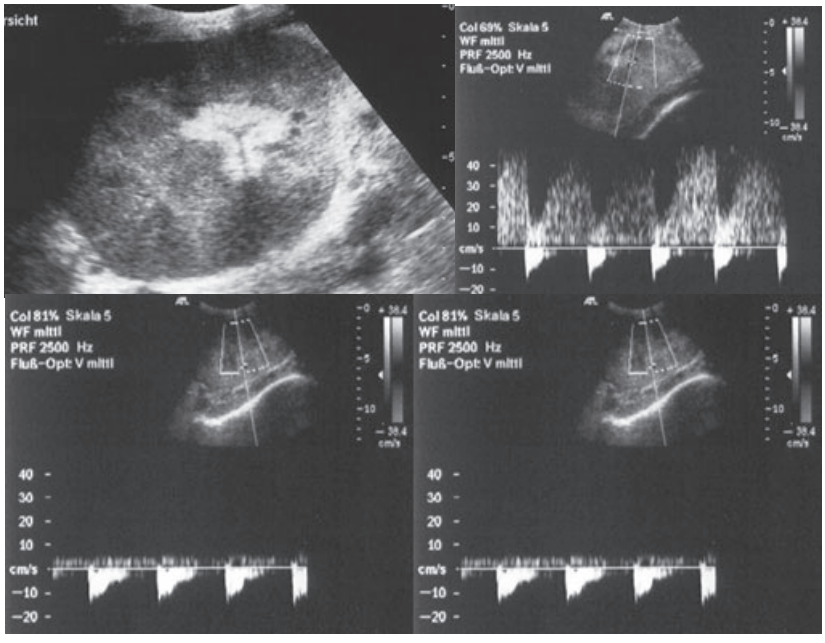


**Figure 1** Ultrasound examination: swollon graft, missing telediastolic signal.

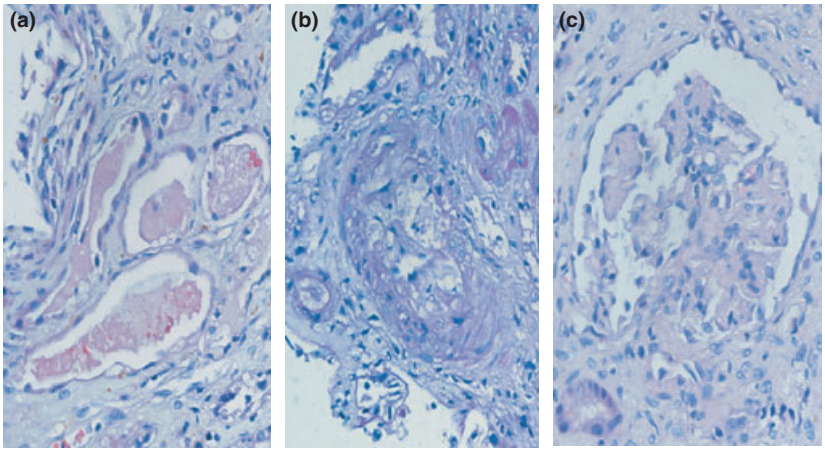


**Figure 2** Renal graft biopsies: (a) first biopsy: 2-day post onset of renal graft failure following steroid bolus and whole plasma exchange: tubular necrosis, interstitial edema and hyalin protein-storage within the tubuli (hematoxylin–eosin magnification ×40); (b) second biopsy: severe thrombotic microangiopathy of glomeruli and arteries with mediolysis within small arteries (periodic acid-schiff (PAS) magnification ×40); (c) third biopsy: microangiopathy with collapsed glomeruli, segmental sclerosis, interstitial fibrosis and tubular atrophy (hematoxylin–eosin magnification ×40).

renal biopsy was performed which demonstrated the late stage of thrombotic microangiopathy with collapsed glomeruli, segmental sclerosis, interstitial fibrosis and tubular atrophy reflecting the recovery from HUS but no signs of rejection (Fig. 2c). Significant improvement of perfusion and absence of graft swelling was demonstrated by ultrasonography. The patient was discharged with a serum creatinine of 4.7 mg/dl in good clinical condition. Creatinine at follow-up 2 months following HUS was 4 mg/dl. Although urinary output ranges between 1000 and 1500 ml/day, the patient requires hemodialysis twice weekly and is currently listed for retransplantation.

## Discussion

Tolerogenic immunosuppressive protocols recently have been favored by many centers to reduce the maintenance immunosuppression [13,14]. The anti-CD52 antibody alemtuzumab has been shown to be effective in prevention of rejection as well as rescue therapy for steroid resistant and even anti-thymocyte globulin-resistant rejection [15,16]. While rejection rates were low using this antibody, less is known about the incidence of other complications. HUS – or thrombotic microangiopathy as referred by some authors – is a rare but severe complication following renal transplantation and can lead to graft loss if not treated adequately [17,18]. It has been described after all types of solid organ transplantation [19–22]. This case suggests that HUS may present in a slightly different way than previously described, following induction with Campath-1H and TAC maintenance therapy. Our patient initially did not develop thrombocytopenia or show fragmentocytes and also histology was largely unspecific and inconclusive. In addition, because of the ultrasound findings, initially humoral rejection was suspected and treated with plasmapheresis. This resulted in subsequent normalization of the graft size and improvement in perfusion and clinical parameters, which led to the wrong conclusion. Because of the massive swelling of the graft on admission and the danger of a rupture, a biopsy was not initially performed but 3 days later. Toxic tubulopathy was suspected because of the histologic findings. However, only after the development of thrombocytopenia, HUS was taken into consideration. Shortly thereafter also fragmentocytes became detectable and histology of a second renal biopsy revealed the typical signs for HUS. The plasma exchange and switch to sirolimus were then able to partially reverse the disorder; however no complete recovery could be achieved and the patient had to be listed for retransplantation.

This is the first case of post-transplant HUS in a patient receiving Campath-1H induction. It should be remembered that HUS may present in an atypical manner when using new immunosuppressants.

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