Transplant International ISSN 0934-0874

ORIGINAL ARTICLE

A cluster of rotavirus enteritis in adult transplant recipients

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Keywords
cyclosporin A, diarrhea, immunosuppression, rotavirus, tacrolimus, transplantation.

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Received: 22 March 2004
Accepted: 26 October 2004

doi:10.1111/j.1432-2277.2004.00073.x

Summary

Diarrhea following solid organ transplantation is a common side effect of some immunosuppressive agents but can also be caused by many pathogens. An outbreak of rotavirus (RV) enteritis presenting with severe diarrhea in four solid organ recipients was analyzed. The first case was diagnosed in a 6-month-old liver recipient who was prehospitalized on a pediatric ward. Within 1 month, three adult patients (two liver, one renal recipient) presented with enteritis. During diarrhea a significant rise in tacrolimus levels was observed. One patient developed toxic megacolon with ulcerative colitis. Infections were self-limiting but led to secondary infectious complications and prolonged hospitalization. This is the first reported outbreak of RV enteritis in a multiorgan transplant unit involving adult patients. Although no fingerprinting or subtyping of the virus was performed we assume the child was the primary source. In transplant recipients presenting with diarrhea RV infection should be considered.

Introduction

Diarrhea following solid organ transplantation can be caused by a variety of infectious agents but is also frequently seen as a side effect of some immunosuppressive drugs, in particular mycophenolate mofetil (MMF) [1]. Common pathogens causing enteritis and colitis in immunocompromised patients are cytomegalovirus (CMV), *Clostridium difficile* and cryptosporidia. However, a variety of other microorganisms including those classical pathogens which cause enteric disease in the healthy host have also been involved [1]. Acute diarrhea represents a worldwide health problem, with rotavirus (RV) being the most common cause of diarrhea in infants and young children in western world [2,3]. The infection usually occurs in 6–36-month-old children and can lead to severe illness requiring hospitalization [2]. In adults, RV is usually only mild. Severe gastrointestinal symptoms, however, have been described in patients under immunosuppression [2–4]. In solid organ recipients, poor general condition, end-stage organ failure combined with surgical trauma and immunosuppressive therapy cause severe impairment of host defense, making these patients prone to a variety of infections including those involving the gastrointestinal tract. Therefore, diarrhea is a frequent complication in solid organ recipients. During diarrhea levels of tacrolimus (TAC) may increase excessively [5]. This was observed specifically during RV-associated diarrhea in pediatric transplant recipients [6–8]. For this reason careful monitoring of TAC levels during diarrhea is mandatory [5,6,8].

We recently observed a cluster of four solid organ recipients (one child and three adults) who developed RV enterocolitis in a multiorgan transplant unit within 1 month of the hospital stay of the child who was first infected with the virus. Epidemiology and clinical impact of this rare complication in adult transplant recipients were analyzed.

Patients and methods

Four patients who underwent solid organ transplantation (three liver, one kidney) and developed RV-associated diarrhea, were included in this retrospective analysis. The

infection was defined as acute gastroenteritis with abdominal pain, diarrhea and proof of RV infection by RV antigen detection from stools using an enzyme-linked immunosorbent assay. Other causes of diarrhea such as antibiotic-associated enteritis were excluded. In addition to RV testing stools were screened for *C. difficile*, *Salmonella*, *Shigella*, *Yersinia*, *Escherichia coli*, and *Campylobacter*. CMV disease was excluded by PCR and pp65 assay. In all cases of RV infection, patients were treated with intravenous fluid replacement and electrolytes, loperamid (Enterobene®; Ratiopharm, Vienna, Austria) and were given an appropriate diet but no antibiotics or antiviral agents. Hospital records of the four patients were analyzed for temperature, weight, stool frequency, leukocyte count, C-reactive protein as well as TAC dosages and TAC trough levels.

Before transplantation all patients were screened for CMV and Epstein–Barr virus (EBV) antibodies and stools were examined for common pathogens such as *Salmonella*, *Shigella*, *Campylobacter*, enteropathic *E. coli*, *Candida* spp. or *C. difficile*, but no screening for rotavirus was performed. Immunosuppressive therapy in this cohort of patients consisted of TAC, MMF or azathioprine and rapidly tapered steroids after induction with an interleukin 2 (IL-2) receptor antibody in three patients.

Hospital and ward setting

Our multiorgan transplant unit includes 22 beds, of which six are for intensive care and two for intermediate care. Between 280 and 330 solid organs are transplanted per year. In 2002 a total of 143 kidneys, 67 livers, 43 pancreases, 26 hearts, 23 lungs, five bowels, eight islet cell grafts were transplanted at this facility.

Results

The first case of RV infection was diagnosed in a 6-month-old liver recipient who was initially hospitalized on a pediatric ward. Within 1 month, three adult patients (two liver, one kidney recipient) also presented with severe diarrhea. The infections were self-limiting, but all patients developed other relevant infectious complications which significantly increased the length of hospital stay.

Elevation of C-reactive protein was observed in all patients during RV enteritis, and three patients presented with pyrexia as high as 39 °C. Increased white blood count was found in the child only. Maximum stool frequency was 10 per day, and diarrhea lasted between 4 and 12 days. In three patients diarrhea was watery, and one patient developed colonic ulcers causing significant blood loss. Fluid supplementation was necessary in all patients and bicarbonate supplementation in two adults. All three adults received loperamid. The patient who developed the most severe diarrhea lost 3 kg within 24 h, which ultimately led to severe dehydration and a drop in blood pressure. In all patients TAC dosage had to be reduced during diarrhea (Fig. 1a, b).

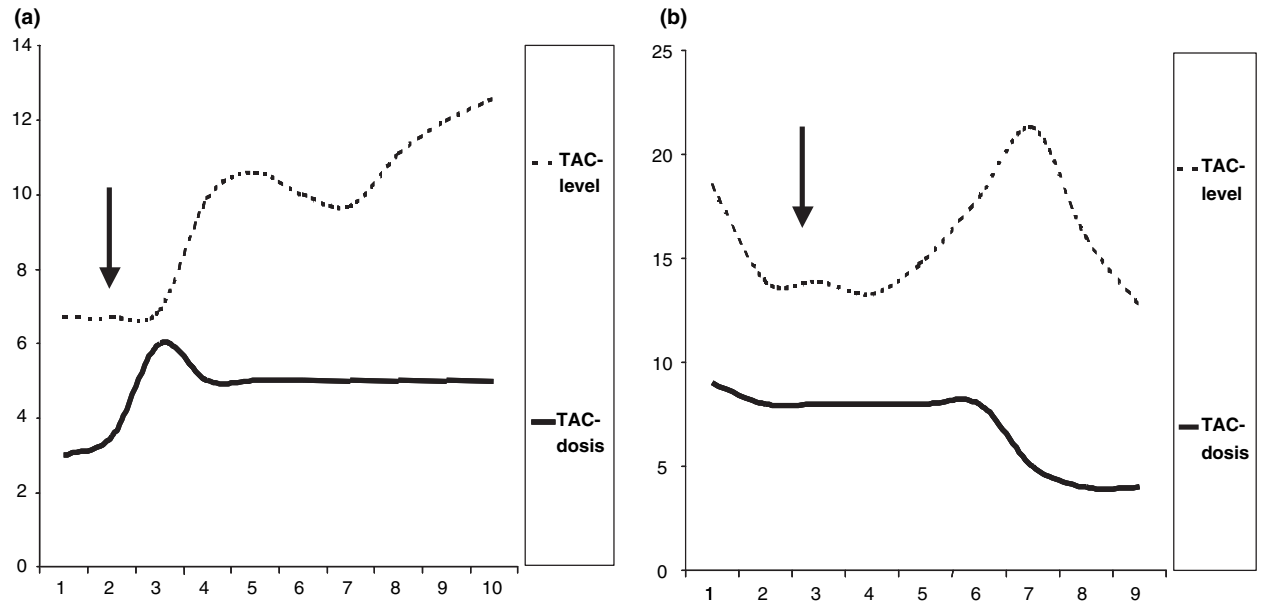

Figure 1 Tacrolimus (TAC) dosage and trough levels during rotavirus enteritis. (a) Significant rise in TAC trough levels after onset of diarrhea (arrow); (b) significant dose reduction.

Case 1 (O. L.)

A 5-month-old boy with biliary atresia received segments II and III from his mother. On day 12 the child had to be retransplanted for hepatic artery thrombosis and was given the left lateral segments of a cadaveric graft. This graft showed excellent initial function. On day 13 postretransplantation an increase in transaminases was observed associated with vomiting and watery diarrhea. TAC was discontinued because of extensive blood levels and restarted at a lower dose after cessation of diarrhea. The patient was transferred from the transplant unit to the pediatric ward 21 days postretransplantation in stable condition with a well-functioning graft.

Case 2 (T. L.)

A 71-year-old male with end-stage renal failure because of polycystic kidney disease received a kidney from his nephew. On day 11 post-transplant, the patient had to be operated for a perforated duodenal ulcer and gangrenous cholecystitis. After recovery from this complication the patient developed toxic megacolon (Fig. 2) with pseudomembranous colitis and was treated with metronidazol. Stool tested negative for *C. difficile* (culture and toxin) but positive for RV. Hemorrhage necessitated transfusion of 4 units of red blood cells. For bacterial and fungal pneumonia cefepime in combination with caspofungin was given. MMF was discontinued to avoid additional gastrointestinal side effects, and the IL-2-receptor antagonist daclizumab (Zenapax®; Roche, Welwyn Garden City, UK) was given. Within 2 weeks, diarrhea ceased and the patient recovered. On day 66 post-transplant the patient again developed diarrhea; colonoscopy revealed recurrent colitis and *C. difficile* was isolated from stool. RV was not identified again and treatment with metronidazol was initiated. On day 182 after transplantation the patient was discharged with stable graft function and a serum creatinine of 1.38 mg/dl.

Case 3 (R.R.)

A 54-year-old male underwent liver transplantation for alcoholic liver disease. Because of poor renal function initial immunosuppression consisted of the IL-2 receptor antagonist basiliximab (Simulect®; Novartis Europharm, Horsham, UK), MMF and steroids without a calcineurin inhibitor. Three weeks post-transplant he developed acute diarrhea, which was empirically treated with metronidazol. *Staphylococcus aureus* was cultured from blood and piperacillin-tazobactam was commenced. Persisting enteritis raised suspicion of gastrointestinal side effects of MMF, which was withdrawn and replaced with azathioprine. Because of impaired renal function cyclosporin A, which was started on day 7, was changed to sirolimus. Shortly after that, RV was isolated from stool specimens. Sirolimus blood level rose to 17 ng/ml and therefore the drug was discontinued for 3 days. Watery diarrhea caused dehydration, electrolyte imbalance and hemodynamic instability requiring ICU treatment. After sirolimus was switched to TAC diarrhea stopped. Diarrhea relapsed during week 6 post-transplant and RV was detected again. Symptoms during this relapse were mild and diarrhea completely stopped on day 57 post-transplant. On day 36 after transplantation, abdominal wall dehiscence had to be repaired. Pleural effusion was drained. *Pseudomonas*

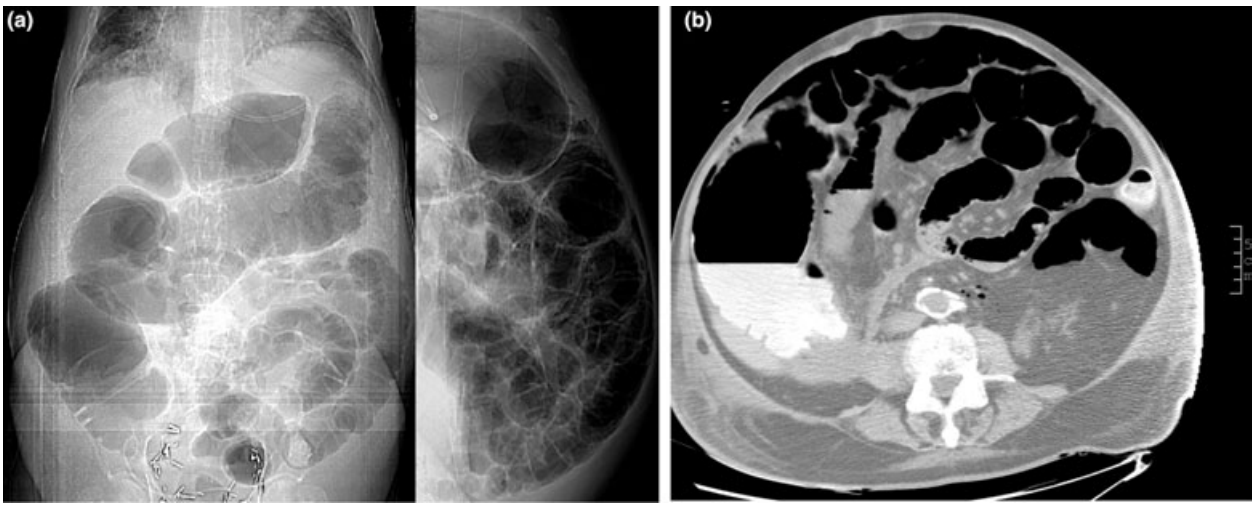

Figure 2 Abdominal CT scan: toxic megacolon because of rotavirus enterocolitis. (a) Anterior–posterior and sagital 'scout' meteoristic colon; (b) enlarged cecum.

aeruginosa was cultured from sputum and cefpirom initiated according to sensitivity. The patient was discharged on day 80 with stable liver function but somewhat impaired renal function.

Case 4 (H. E.)

The 51-year-old male patient underwent liver transplantation for hepatitis C-associated cirrhosis. Immunosuppressive therapy consisted of an IL-2 receptor antagonist with TAC and methylprednisolone. RV enteritis occurred 3 weeks after liver transplantation. Diarrhea stopped within 1 week under conservative management. During diarrhea, TAC trough levels peaked to 21.3 ng/ml with 8 mg/day and TAC dosage was reduced by 50%, which resulted in trough levels of 11 ng/ml. During the second week after surgery the patient developed staphylococcal sepsis, which was treated with cefuroxim. A superficial wound infection with isolation in *Klebsiella pneumoniae*, *Citrobacter freundii* and *S. aureus* prompted a change of the antibiotic regime to ciprofloxacin. Three weeks post-transplant during RV enteritis *S. aureus* was again isolated from blood cultures. This episode of sepsis was successfully treated with clindamycin. The patient experienced a third episode of staphylococcal sepsis during week 5 post-transplant. Echocardiography revealed endocarditis of the aortic valve with large vegetations. Aortic valve replacement using a biological prosthesis was performed and the patient received cefuroxim, fosfomycin and clindamycin. He was discharged on day 61 post-transplant with good liver allograft function and stable cardiac function and with no signs of infection.

All other patients who were hospitalized on the ward during the outbreak were tested for RV. The four described individuals, however, were the only infected patients. During a 6-month follow-up only one more sporadic case of RV infection occurred. After a follow-up of 6 months all four patients are alive with well-functioning grafts.

Discussion

Infection is the most common complication after solid organ transplantation. Diarrhea is a common side effect of immunosuppressive drugs such as MMF and sirolimus, but has also been associated with antibiotics [1,5–8]. In immunocompromised patients numerous microbes including viruses such as CMV and EBV as well as bacterial, protozoal and fungal pathogens may cause enteric infection [1].

Rotavirus is the most common pathogen causing diarrhea in children, not only in developing countries but also in the western world. In the United States approximately 2.7 million children younger than 5 years of age are affected by RV diarrhea each year, resulting in 500 000 physician visits and 50 000 hospitalizations with an estimated $ 274 million in medical care [3]. In Austria, the incidence of community-acquired acute RV gastroenteritis is 1.33 per 100 children per year, and for nosocomially acquired RV infection 2.59 per 1000 hospital days [6]. Thus far, only few data are available on RV infections in solid organ transplant recipients. Normally, RV is an unpleasant but harmless infection in adults. In transplant recipients it may be associated with a more severe disease causing extensive fluid, electrolyte or even enteric blood loss and an increase in immunosuppressive drug levels [1,2].

Tacrolimus is a potent immunosuppressive drug frequently used in liver transplantation [5–8]. During diarrhea a significant increase in trough levels of TAC in pediatric transplant recipients has been reported [5]. Possible explanations for the rise in blood levels of TAC could be increased absorption as a result of increased intestinal permeability or reduced hepatic metabolism caused by reduced hepatic blood flow, hepatic dysfunction or hemoconcentration [7]. Therefore, daily monitoring and early dose reduction have been recommended to prevent severe side effects such as nephrotoxicity and neurotoxicity and, most importantly overimmunosuppression with opportunistic infections, and also to prevent rejection after dose reduction [5–8].

Treatment of RV enteritis includes oral or intravenous rehydration with replacement of electrolytes and dietary measures. In most patients the disease is self-limiting. Thus far, no specific agent against RV has been found and administration of oral immunoglobulins is controversially discussed [9]. During the early post-transplant period watery diarrhea may cause severe hypovolemia, and hemorrhagic enteritis or colitis may be associated with significant blood loss necessitating blood transfusions [4]. Hence, it seems that prevention of RV infection may represent the only effective measure in transplant recipients. Vaccination against RV might be an option for the future. In the United States a vaccine was licensed in 1998, and in clinical trials in industrialized countries 49–68% protection against any RV diarrhea and 61–100% protection against severe disease was achieved [3]. Thus far, no data on the effectiveness of the vaccine in immunocompromised patients are available. This outbreak demonstrates the risk of RV transmission from infants to immunocompromised adult patients on a transplant ward. As RV infection is very common in the pediatric population, an effective means of prevention could be the isolation of this patient group on transplant wards. If strict isolation is not possible, stool in infants should be tested for RV on a regular basis [4].

To the best of our knowledge, this is the first report demonstrating the possible risk of RV transmission from pediatric patients to immunocompromised adult recipients on transplant wards. Although rare, it can be a severe complication associated with a dramatic rise in blood levels of TAC. Thus, careful monitoring and early dose reduction to avoid severe complications are mandatory. For effective prevention, we recommend isolation of the pediatric population on a transplantation unit or routine screening for RV infection. Vaccination may be a possible means of preventing outbreaks of RV in immunosuppressed adult patients.

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