Exceptional Case

Chronic norovirus infection in renal transplant recipients

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Abstract
Norovirus infection is the most common cause of acute gastroenteritis. In immunocompetent subjects, norovirus infection is a self-limiting disease of short duration. The present report provides first evidence that norovirus can cause chronic infection in renal transplant recipients. Two patients showed persisting norovirus excretion for >7 months and 3 months, respectively. The first patient was asymptomatic after an acute episode of gastroenteritis and eliminated the virus spontaneously. The second patient developed severe symptomatic chronic infection with diffuse abdominal discomfort, fever, transient transplant dysfunction, recurrent episodes of diarrhoea, weight loss and histological signs of chronic intestinal inflammation. Norovirus elimination and relief of symptoms occurred only after reduction of immunosuppression. Thus, norovirus can evoke asymptomatic and symptomatic chronic infection in renal transplant recipients. Norovirus should therefore be considered in the differential diagnosis of both acute and chronic diarrhoea after transplantation. Reduction of immunosuppression may be indicated to allow virus elimination in symptomatic cases.

Keywords: gastroenteritis; immunosuppression; norovirus; transplantation

Background
Norovirus infection is the most common cause of acute gastroenteritis. The classical clinical presentation of norovirus infection is characterized by a self-limited short-term (usually 24–48 h) episode of gastroenteritis with massive watery diarrhoea, nausea and vomiting. At present, little is known about the presentation of norovirus infection in renal transplant recipients. Does immunosuppression aggravate the clinical presentation of this usually harmless ‘gastric flu’ regarding duration and intensity of its symptoms? In the following, we present the first description of two renal transplant recipients who developed chronic norovirus infection.

Results
A 73-year-old male presented to our hospital with watery diarrhoea, nausea and vomiting for <24 h. The patient had a history of cadaveric renal transplantation 3 months earlier due to Wegener’s granulomatosis-associated end-stage renal failure. Immunosuppression consisted of cyclosporine, mycophenolate mofetil (MMF) and prednisolone. One day after the beginning of his symptoms, his wife developed diarrhoea and vomiting as well. Norovirus infection (genogroup II) was diagnosed from stool reverse transcriptase PCR (RT-PCR, PCR format including genogroup differentiation according to Hoehne & Schreier [1]). Stool specimens were negative for clostridium difficile toxine A and B, salmonella, shigella, yersinia, campylobacter and parasites. Within 4 days the diarrhoea resolved spontaneously. Five and a half months later we repeated norovirus RT-PCR, which turned out to be positive again. As the patient did not have any complaints, immunosuppression was continued without any changes. In a control examination 7.5 months after initial diagnosis, the PCR testing of stool specimens was negative for norovirus RNA. Another 73-year-old male was admitted to our hospital with watery diarrhoea, nausea and vomiting after contact with three ill persons. The patient had a history of living donor renal transplantation 14 years previously for end-stage renal failure of unknown origin. The immunosuppressive regimen consisted of tacrolimus, MMF and prednisolone. Stool specimens were negative for clostridium difficile toxine A and B, salmonella, shigella, yersinia, campylobacter and parasites. Within 4 days the diarrhoea resolved spontaneously. Five and a half months later we repeated norovirus RT-PCR, which turned out to be positive again. As the patient did not have any complaints, immunosuppression was continued without any changes. In a control examination 7.5 months after initial diagnosis, the PCR testing of stool specimens was negative for norovirus RNA.
gastroenterologist for diffuse abdominal pain. Deep duodenal biopsies were negative for CMV infection and Whipple’s disease but revealed broadened and shortened villi and acute and chronic inflammatory cells in the lamina propria (Figure 1A) and CD8+ intraepithelial T lymphocytes in the upper normal range (34 per 100 enterocytes, normal range <40 per 100 enterocytes, immunostaining with antibody clone C8/144B, Dako, Glostrup, Denmark; Figure 1B).

Two months after the first episode of symptomatic norovirus infection, the patient was admitted to our hospital again with diarrhoea, dehydration and fever of 39°C. His baseline creatinine of 124 µmol/l increased to a maximum of 186 µmol/l. White blood cell count was normal, but CRP increased to 82 mg/l. In an intensive diagnostic workup including chest x-ray, abdominal sonography, x-ray of the paranasal sinuses, CMV-PCR and transesophageal echocardiography, no other infectious focus was identified. The patient was discharged after 15 days. At this time, he was still in reduced general condition but had no diarrhoea or fever anymore.

Ten days later, he suffered from diarrhoea again, was in poor clinical condition and presented with a weight loss of >5 kg and hypoalbuminaemia. Norovirus-PCR for genogroup II was positive at each admission. Thus, norovirus excretion was documented for a period of 3 months. Biopsies from duodenal mucosa were retrieved again (Figure 1C/D). At this time, the patient developed acute transplant failure. We reduced immunosuppression to MMF and prednisolone; tacrolimus was withheld. Within the next 2 weeks, the patient’s condition improved markedly: fever, transplant failure and diarrhoea disappeared, he gained 5 kg of weight and was without any complaints. Norovirus-PCR turned out to be negative.

**Discussion**

In immunocompetent subjects, norovirus infection is a self-limiting disease of short duration. Asymptomatic virus shedding may be prolonged e.g. in geriatric subjects, children and hospitalized patients [2–7]. Symptomatic chronic disease, however, has not been described in immunocompetent subjects so far. Our first patient showed asymptomatic norovirus excretion for 6 months but eliminated the virus without reduction of immunosuppression. The second patient suffered from recurrent episodes of diarrhoea, abdominal pain and fever for >3 months. Virus elimination occurred only after reduction of immunosuppression. Thus, norovirus can cause both asymptomatic and symptomatic chronic infection. In both cases, patients have to be regarded as infectious and hygienic strategies are required to prevent infection of contact persons. Our observations are limited by the lack of sequencing analyses of the viral genome. Therefore, subclinical reinfection with different viral strains cannot be finally excluded. Future studies on norovirus infections in immunocompromised patients should include sequencing of viral amplicons.

The histological examination of deep duodenal biopsies revealed a partial villous atrophy and chronic inflammatory cells in the lamina propria indicating chronic small bowel...
inflammation. With regard to the severe clinical presentation, it is surprising that the number of CD8+ intraepithelial T-cells was in the (high) normal range at initial examination. Intraepithelial cytotoxic T-cells are regarded as a prerequisite for virus elimination [8]. It may be speculated that the patient’s immunosuppression might have prevented a more intense intraepithelial infiltration with T lymphocytes resulting in an inability to eliminate the virus.

Chronic norovirus infection has been described in pediatric intestinal transplant recipients [9–11]. Furthermore, chronic excretion of norovirus has been reported in a heart transplant recipient and in a child with cartilage hair hypoplasia following bone marrow transplantation [12,13].

Our findings show that the clinical presentation of norovirus infection in transplant patients differs from its typical form concerning not only the duration of the infection but also the intensity of symptoms. It can cause a highly febrile condition with markedly elevated CRP and acute renal failure resembling the clinical features of bacterial infection. Notably, our symptomatic patient did not suffer from diarrhoea continuously. There were transient periods with diffuse abdominal discomfort in the absence of diarrhoea or nausea. Thus, the diagnosis of chronic norovirus infection might be difficult and should be kept in mind in cases of persisting abdominal complaints in transplant patients after an acute episode of gastroenteritis.

The present report is the first description of a chronic norovirus infection in renal transplant recipients. Norovirus infection should be considered in the differential diagnosis not only of acute but also of chronic diarrhoea in transplant recipients. Reduction of immunosuppression may be indicated to allow virus elimination in symptomatic cases.

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References


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