



Sapovirus-Associated Diarrhea in Renal Transplant Patient Treated without Altering Immunosuppression

Abstract

Solid organ transplant (SOT) recipients are at increased risk of infective diarrheas. In such patients, diarrhea can be complicated by dehydration, leading to acute kidney injury or vascular thrombosis. Viral diarrhea in SOT is reported to be commonly due to cytomegalovirus and norovirus. As sapovirus is not routinely included in diagnostic evaluations, its epidemiology and natural history is not well documented. Anecdotal cases of sapovirus-associated diarrhea in renal transplant recipients have been treated with oral nitazoxanide, often with simultaneous reduction in immunosuppressants. We report sapovirus-associated diarrhea in a renal transplant recipient which responded well within two days to oral nitazoxanide. This, possibly, is the first such report from the Indian subcontinent of adequate control of sapovirus-associated diarrhea without any alteration in the immunosuppressant medications.

Keywords: *Sapovirus, Diarrhea, Transplant recipients, Nitazoxanide, Immunosuppressant*

Introduction

Chronic immunosuppression increases the risks of infectious diarrhea among solid organ transplant (SOT) recipients. Common viral etiologies include cytomegalovirus and norovirus. As more sensitive diagnostic tools become available, emerging causes of viral enteritis are being identified. We present a renal transplant recipient with sapovirus-associated diarrhea treated successfully using nitazoxanide.

Case Report

In September 2014, a 17-year-old girl with history of chronic kidney disease stage 5 secondary to biopsy-proven chronic tubulo-interstitial nephritis had received a live related renal transplant. She was on triple-drug immunosuppression and maintained stable serum creatinine levels at 1.2 mg/dL. In April 2023, at 26, she presented to our outpatient department with two weeks of diarrhea. She was passing 6–8 stools daily and said it had started after consumption of around 100 mL of palm wine called 'kallu' or 'toddy' locally. Stools were watery, whitish to yellowish, and of medium volume. There was occasional abdominal cramping but no fever, nausea or anorexia. She was managed with loperamide and ricedotril without much relief. Probiotics were avoided to prevent superadded infections by *Lactobacilli*, *Bifidobacterium*, *Peptostreptococci*, etc.

In May 2023, she was admitted for closer monitoring and intravenous fluid management. At admission, her vitals were normal with no pallor, icterus, cyanosis, lymphadenopathy, or edema. She was clinically volume depleted. The serum creatinine was 1.9 mg/dL. Stool routine microscopy showed no parasitic ova or cysts and stool culture showed no pathogenic bacterial growth. The BioFire FilmArray™ gastrointestinal panel of polymerase chain reaction (PCR) tests was positive for sapovirus and Shiga toxin producing *E. coli* (STEC)/*E. coli* O157. Supportive

care with intravenous fluids was continued and tablet nitazoxanide 500 mg twice daily was started. Within two days, the stool frequency reduced and serum creatinine level returned to 1.2 mg/dL. Nitazoxanide was continued for a total of seven days. Immunosuppression therapy was not altered.

Discussion

Sapovirus, like norovirus, is a small, single-stranded RNA virus of the Caliciviridae family. While norovirus accounts for 90% of gastroenteritis outbreaks among adults worldwide, neither of the viruses is very well-studied in the immunocompromised population.¹

We found only one multiplex PCR comparison of the infective etiology of diarrhea among renal transplant patients and non-transplant patients from the Indian subcontinent.² The commonest cause was bacterial infection. Individually, among transplant patients, norovirus was the most common organism isolated. In contrast, sapovirus was detected during only one of the 304 diarrhea-related hospitalizations (in both transplant and non-transplant groups) analyzed.

Though the presentation is very similar to norovirus infection, there are scanty reports of sapovirus-associated diarrhea in renal transplant.^{1–5} One treated case of norovirus-associated diarrhea has also been reported where a superimposed sapovirus infection developed.⁶

Compared to bacterial and parasitic infections, norovirus/sapovirus infections are associated with greater weight loss, longer duration of symptoms, and more frequent need to reduce the dose of immunosuppressants.³ This can potentially cause graft dysfunction and rejection. A large proportion of patients experience acute kidney injury. Some cases of biopsy-proven active graft rejection and oxalate nephropathy have also been reported. Viral shedding in stool, in some cases, lasted up to 581 days.³

Due to lack of specific therapies for STEC and viral diarrhea, management focuses on hydration and antimotility agents. In SOT patients, dose of immunosuppressants is often reduced on diagnosis of norovirus or sapovirus, in order to help control the infection and prevent superadded infections. A fine balance is needed between managing the infection and preventing graft dysfunction. Some researchers suggest “an alternative management plan with use of oral nitazoxanide”¹

Nitazoxanide, a thiazolide, has antibacterial, antiviral, and antiparasitic properties. Given orally, it inhibits viral replication in the intestinal mucosa probably by targeting cellular pathways in the synthesis of viral proteins.¹

We had used the same dose as Ghussou and Vasquez¹ who demonstrated a negative sapovirus PCR in a repeat stool

infectious panel one month after nitazoxanide therapy [Table 1]. In our patient, the diarrhea improved within two days—a day earlier than their patient. They had gradually tapered and discontinued the immunosuppressant mycophenolate mofetil and replaced it with azathioprine. We were able to safely and successfully control sapovirus-associated diarrhea with oral nitazoxanide without reducing the immunosuppression. There possibly is only one earlier report of sapovirus diarrhea successfully treated with nitazoxanide without reducing immunosuppression.⁵ The chronic norovirus and subsequent sapovirus diarrhea reported by Wright *et al.*⁶ required prolonged treatment with nitazoxanide and reduction of immunosuppression leading to graft rejection. That patient as well as the one managed by Ghussou and Vasquez,^{1,6} had substantial unplanned weight loss before the PCR-based diagnosis.

Table 1: Sapovirus diarrhea cases successfully treated with oral nitazoxanide

Study	Age (y) & sex	Time since transplant	Signs, symptoms, & lab findings at admission	Treatment	Outcomes	Remarks
Ghussou & Vasquez, ¹	30 F	10 y	4–5 stools/d; ↑ creatinine; 15 lb unintentional weight loss; ↓Hb	IV fluids; antidiarrheals; NTZ 500 mg orally twice daily for 7d	Diarrhea improved within 3d of NTZ; Sapovirus -ve PCR in 1 mo after therapy	MMF dose ↓ & stopped - replaced with AZT;
Myat and May, ⁵	32 F	11 mo	Frequency of stool NR; ↑ creatinine	NTZ for 3d (dose NR); Supportive care NR	Resolution of diarrhea; Return to baseline creatinine; Rapid resolution of Sapovirus PCR (time to PCR negativity NR)	No reduction of immunosuppression; timeline of resolution of diarrhea NR; Time of repeat PCR is NR.
Present Case	26 F	9.5 y	6–8 stools/d; ↑ creatinine; No pallor	IV fluids; antidiarrheals; NTZ 500 mg orally twice daily for 7d	Diarrhea improved within 2d of NTZ	No reduction of immunosuppression

NTZ: nitazoxanide; PCR: polymerase chain reaction; MMF: Mycophenolate mofetil; AZT: azathioprine; NR: not reported; Hb = hemoglobin; IV = intravenous

Conclusion

Stool PCR, if available, should be done for all SOT patients presenting with diarrhea. Though it is more expensive than conventional tests and cannot differentiate active and asymptomatic carriers, in transplant patients where risks are higher, delays in diagnosis should be avoided. We also suggest adding nitazoxanide to the treatment regimen without reducing immunosuppression.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

Conflicts of interest

There are no conflicts of interest.

Ravi Andrews¹ , Mohammed Sajid Abdul Samad¹, Teja Chintalapudi¹, Venkat Ramesh², Muna Ather Ali³
 Departments of ¹Nephrology, ²Infectious Diseases, ³Critical Care Medicine, Apollo Health City, Hyderabad, India.

Corresponding author:

Ravi Andrews, Department of Nephrology, Apollo Health City, Hyderabad, India. E-mail: raviandrews@rediffmail.com

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