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Case report

Persistent *Norovirus* infection in a young patient with renal transplant: The challenging cost of immunosuppression and the negative impact on patient's quality of life

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ABSTRACT

Norovirus (NoV) is one of the most common causes of acute infectious gastroenteritis in the United States (US). The infection is typically short-lasting and self-limiting in immunocompetent hosts. Renal transplant recipients on immunosuppressive therapy are more prone to infectious gastroenteritis that can be caused by various common and opportunistic organisms. NoV infection in renal transplant patients presents as an acute diarrheal illness that may progress to a chronic infection with frequent relapses leading to adverse short-term complications (acute renal injury (AKI) and acute graft rejection from the reduction of the dose of immunosuppressive medications) and possibly long-term morbidities (malabsorption syndrome, and a decline in graft survival). The management of chronic NoV infections in renal transplant patients may be quite challenging, as no specific antiviral treatment is presently approved, and frequent adjustments of immunosuppressive therapy may be required in the setting of reduced renal clearance and the attempts to decrease immunosuppressive effects to enhance the viral clearance.Herein, the authors present a case of persistent NoV in a young female patient with a renal transplant that was associated with recurrent admissions with AKI, gross electrolyte disturbances, and significant weight loss. The relapsing NoV infection has negatively impacted the patient's quality of life and socioeconomic performance.

Introduction

Norovirus (NoV) is one of the leading causes of acute infectious gastroenteritis globally, accounting for about 20 % of cases worldwide [1], and it accounted for more than 50 % of foodborne infections in the US according to the Center for Disease Control and Prevention (CDC) in the year 2013 [2]. The first case of *norovirus*-associated acute gastroenteritis was described in Norwalk, Ohio in 1968 [3]. The infection spreads through the fecal-oral route and is highly contagious [3]. *Norovirus* is a non-enveloped single-stranded RNA virus from the *Caliciviridae* family [3]. Five genotypes were discovered (GI to GV) [3]. Most of the outbreaks are caused by GII.4 strains [4].

NoV infection is typically self-limited and short-lasting in immunocompetent hosts [4], however, immunocompromised patients may suffer from more-severe acute diarrheal illnesses with a risk of progression to a chronic infection due to impaired viral clearance [4]. The renal transplant recipients on immunosuppressive therapy are more vulnerable to infectious diarrheal diseases from various organisms due to the iatrogenic immunodeficiency state [5]. NoV infection is an emerging challenge among the renal transplant population, as it can lead to severe acute illness as well as chronic relapsing infection that may be associated with adverse short-term outcomes (AKI and acute graft rejection) and possibly long-term morbidities (malabsorption syndrome, and reduced graft survival) [5–9].

Herein, the authors described a persistent NoV infection in a young patient with a renal transplant that was associated with recurrent admissions with AKI, gross electrolyte disturbances, and significant weight loss, which negatively impacted the patient's quality of life and socioeconomic performance. The infection has also posed a therapeutic challenge to the providers. The current literature on the clinical

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presentation and outcome of NoV infection in renal transplant recipients was briefly summarized in this communication.

Case presentation

A 26-year-old female with a past medical history of a deceased donor kidney transplant nine years ago (due to end-stage renal disease from renal hypoplasia of unknown etiology) on tacrolimus (2 mg BID) and mycophenolate mofetil (MM, 500 mg BID), hypertension, and pancytopenia who presented to the emergency room with diarrhea and loss of appetite for two weeks. The patient reported watery diarrhea with no blood or mucus and a frequency of four to five times daily for the last 10 days. The patient also reported nausea and loss of appetite for the same duration. The patient has regular follow-ups with her primary nephrologist and the renal transplant consultant at a tertiary transplant center, and she endorsed regular compliance with her immunosuppressive medications. No sick contacts or recent antibiotic use.

Physical examination was noticeable for a thin female with a low body mass index (BMI) of 16.3 kg per square meter, dry mucus membranes, and conjunctival pallor. Vital signs showed blood pressure of 100/55 mmHg, pulse rate of 120 beats per minute, respiratory rate of 18 breaths per minute, and temperature of 98.5 F. The rest of the systemic examination was unremarkable.

Initial laboratory evaluation revealed a hemoglobin of 7.7 g/dl (reference range 12–15.3 g/dl), white blood cell counts of 2.7 $\times$ 10^3 cells/mm cubic (reference range 4.0–11.0 $\times 10^3$, absolute lymphocytes count 0.6 k/ mm cu), platelets of 111 $\times$ 10^6 cells/mm cubic (reference range 150–450 $\times$ 10^6), all around her baseline values. The comprehensive metabolic panel (CMP) revealed creatinine of 1.87 mg/dl (patient's baseline creatinine was 1.2 mg/dl, reference range 0.6–1.3 mg/dl), serum sodium of 128 mmol/L (range 130–145 mmol/), serum potassium of 2.9 mmol/L (range 3.5–5.2 mmol/L), and serum magnesium of 1.4 mmol/L (range 2.2–2.6 mmol/L). The tacrolimus level was within the therapeutic range. Stool analysis was negative for leukocytes, red blood cells, ova, and parasites. *Clostridium difficile* antigen and toxins assays were negative. Stool cultures were negative for commonly encountered bacterial and parasitic pathogens associated with acute diarrhea (including *Campylobacter, Escherichia coli, Salmonella,* and *Cryptosporidium*). Stool polymerase chain reaction (PCR) was positive for *Norovirus* GI/GII.

The patient's symptoms gradually improved over a few days with supportive management. The tacrolimus dose was adjusted to 1.5 mg BID to avoid toxicity in the setting of reduced eGFR clearance and to enhance the viral clearance per discussion with nephrology and infectious disease services. The patient was discharged safely with regular follow-up with her primary renal transplant service after resuming her regular tacrolimus dose with normalization of the renal function.

The patient had three further hospitalizations with relapsing non-bloody diarrhea, progressive weight loss, and significant electrolyte deficits due to stool PCR-confirmed *Norovirus* GI/GII. Extensive diagnostic investigations, including esophagogastroscopy and colonoscopy with serial biopsies, did not reveal any underlying causes of the patient's symptoms. Table 1 summarizes the recurrent admissions with the patient's recorded weight, renal function, and the outcome of each admission. The second admission to our facility was complicated by an AKI, and further evaluation with a renal biopsy ruled out active graft rejection but revealed acute tubular necrosis (ATN). Frequent adjustments of tacrolimus and MMF dosages were warranted during those admissions. The fourth admission was complicated by an acute depressive episode that was partly attributed to recurrent hospitalizations and income loss, and she was started on an antidepressant with outpatient psychiatry follow-up.

The patient was commenced on nitazoxanide 500 mg BID for four weeks to minimize the future recurrence of NoV infection following the fourth admission. The patient remained symptom-free on serial follow-ups at least for four months (at the time of writing this report).

Discussion

Recent studies reported that less than one-fifth (18 %) of infectious gastroenteritis in the solid organ transplant (SOT) population was caused by *norovirus* [13,14]. The clinical course of NoV in transplant recipients distinctly differs from its natural history in immunocompetent hosts, not only in the duration of the infection but also in the severity of

Table 1
A summary of the patient's recurrent admissions with relapsing NoV infection demonstrating the length of stay (LOS), recorded weight at each visit, renal function, and the outcome of each admission.

Admission date (month/day/year)	1/25/2022	9/12/2022	11/4/2022	12/14/2022
Length of stay (LOS)	8 days	6 days	7 days	5 days
Recorded weight per kilogram	47.5 kg	37 kg	32.7 kg	29 kg
Average creatinine level (mg/dl) (Reference range 0.60–1.30 mg/dl)	1.75 mg/dl	1.96 mg/dl	1.92 mg/dl	1.76 mg/dl
Admission course and outcome	Norovirus detected on stool PCR. Received supportive treatment along with a reduction of immunosuppressive medications. Discharged home with a trial of NTZ for 2 weeks but she was unable to get the prescription as it was not available at local pharmacies.	Norovirus detected on stool PCR. The patient was neutropenic during this admission with a neutrophil count of 450 cells/mm cubic. The patient also had severe non-anion gap metabolic acidosis from diarrhea and was started on bicarbonate tablets. Symptoms of Diarrhea and pancytopenia improved after the reduction of her immunosuppressive medications.	Norovirus detected on stool PCR. The patient had pancytopenia at her baseline values. Had severe non-anion gap metabolic acidosis from diarrhea and the resultant acute kidney injury. The patient received supportive management along with a reduction of her immunosuppressive medications with a resultant resolution of her symptoms. NTZ was prescribed on discharge, but it was denied due to insurance issues.	The patient had acute watery diarrhea. The patient received supportive management along with a reduction of her immunosuppressive medications with a resultant resolution of her symptoms. She was discharged on NTZ 500 mg BID for four weeks. The patient did take the full course on serial follow-up as an outpatient.

symptoms [10]. NoV infection can be chronic with periods of exacerbation of symptoms as shown in our patient who suffered recurrent relapses requiring frequent admissions [11]. The clinical presentation in immunocompromised patients is usually characterized by high-grade fevers and elevated inflammatory markers. and the occurrence of AKI that mimics the clinical picture of bacterial syndromes [10].

The pathogenesis of NoV involves viral binding to enterocyte-specific antigens, cellular edema, and enterocyte cell injury resulting in severe diarrheal illness in immunosuppressed patients [13]. Impaired B-cell and T-cell-mediated-viral clearance due to an iatrogenic immunosuppression state results in prolonged viral shedding [9,10]. This pattern of chronically relapsing disease may be partly explained by viral evolutions in immunocompromised hosts, genomic diversity, and the present lack of efficient anti-viral therapy [13].

The intractable diarrheal illness with recurrent acute flare-ups in our patient resulted in ongoing electrolytes disturbances and significant weight loss from malabsorption syndrome. Extensive diagnostic work-up has not yielded other etiologies to explain the patient's symptoms. The frequent hospitalizations of our young patient led to profound psychosocial morbidity that necessitated social worker and psychiatry services evaluation, consistent with the literature that describes an impaired quality of life in the renal transplant population who experience recurrent gastrointestinal symptoms [15].

Per the literature review, five similar cases of chronic NoV in post-renal transplant patients were comparable to our presented patient [10–12]. Table 2 summarizes those patients' demographic features, clinical presentation, reported complications, management, and outcome. The occurrence of AKI from ATN observed in our patient was reported in similar patients [10–12]. The etiology of AKI in those patients was multifactorial from severe dehydration, hypotension, superimposed bacterial sepsis, tacrolimus toxicity, virus-induced ATN, and acute graft rejection that may potentially complicate a reduction of the dose of immunosuppressive therapy [12].

Tacrolimus toxicity from dehydration and reduced eGFR usually warrants a temporary holding or dose reduction [10–12]. The supra-therapeutic levels of tacrolimus may also be caused by a disruption of the P-glycoprotein efflux pump associated with diarrheal diseases [12]. An adjustment of immunosuppressive therapy is often required to avoid drug toxicity and reduce the severity and duration of symptoms by improving viral clearance [10–12]. Nevertheless, it should be carefully balanced with the potential risks of precipitating acute graft rejection, as reported in one patient [12].

Five cohort studies from the USA [5], Germany [6,7], and France [8,9] reported on the epidemiology, clinical features, short and long-term outcomes, and management of NoV infections in patients with a renal transplant. Table 3 summarizes these studies. The retrospective study authored by Avery et al., 2016 [5] reported that about 31 out of 193 (16 %) transplant recipients tested positive for stool NoV PCR. AKI occurred in 23 % and persisted in 21 % after 6 months. The median duration of diarrheal symptoms was 4 months (range, <1–20), and 11/31 (35.4 %) of patients had relapsed after improvement [5]. A prospective cohort conducted by Gackler et al., 2022 [6] included 60 renal transplant patients with NoV infection, 48 % [29] had acute NoV infection only, and 52 % [31] progressed to chronic NoV infection. For patients with chronic NoV infection, LOS was significantly prolonged ($P = 0.024$). Renal allograft function remained impaired in the chronic NoV group at 6 and 12 months after initial admission [6].

Three cohorts compared patients and control groups regarding the

Table 2
A summary of the literature review of case reports of acute and chronic NoV infections in patients with renal transplant 2009–2022.

Study	Year	Gender	Age (years)	Status of renal transplant	maintenance Immunosuppressive medications	Clinical presentation	Outcome
Westhoff et al., [10]	2009	Male	73	Cadaveric renal transplantation 3 months earlier due to Wegener's granulomatosis.	Cyclosporine, mycophenolate mofetil (MMF), and prednisolone.	Acute diarrheal illness with positive stool PCR for NoV	Acute diarrhea resolved after 4 days with conservative management. Continued immunosuppressive therapy. Repeat stool PCR after 4.6 months was still positive for NoV but the patient was asymptomatic, stool PCR was then negative at 7.5 months.
Westhoff et al., [10]	2009	Male	73	Living donor renal transplantation 14 years previously for an end-stage renal failure of unknown origin.	Tacrolimus, MMF, and prednisolone	Three episodes of acute diarrheal illness due to NoV over three months. The last admission was complicated by AKI and significant weight loss, so tacrolimus was temporarily held.	All episodes resolved within 5–15 days with conservative management. Repeat stool PCR was negative after the last episode.
Wright et al., [11]	2020	Male	68	Bilateral native kidney nephrectomies for renal cell carcinoma	MMF, tacrolimus, and prednisone	Chronic diarrhea (> 6 weeks) due to NoV with AKI and elevated tacrolimus. Two relapses at 2 months and 5 months later.	The first episode was treated with nitazoxanide for 2 weeks with clinical resolution. The second episode was treated with nitazoxanide for 6 weeks
Ghusson et al., (212)	2018	70	Female	Cadaveric renal transplantation for streptococcal GN five years prior to presentation	Tacrolimus, MMF, and prednisolone	Chronic diarrhea due to NoV with AKI. MMF was replaced by azathioprine. Second admission with acute diarrheal illness after 2 months with positive stool PCR for NoV	The first episode was treated with nitazoxanide for 3 days with a clinical improvement. The second episode was treated with nitazoxanide for 3 weeks. The third episode was treated with higher doses (500 mg POD three times daily instead of twice) for 3 weeks with clinical and laboratory resolution of NoV infection.
Ghusson et al., [12]	2018	78	Male	Cadaveric renal transplantation for diabetic nephropathy three years prior.	tacrolimus, MMF, and prednisolone at higher doses due to chronic graft failure before 2 years.	Acute diarrheal illness due to NoV with AKI requiring emergent hemodialysis. The disease course was complicated by acute graft rejection presumably from a reduction of immunosuppressive therapy.	Treated with nitazoxanide for 14 days, as diarrhea failed to resolve after the initial 3-day course. The patient lost follow-up, so repeat stool PCR testing was not available

Table 3
A summary of the literature review of cohort studies of acute and chronic NoV infections in patients with renal transplant 2009–2022.

Study	Year	Country	Study design	Results
Avery et al., [5]	2016	USA	Retrospective study	Thirty-one of 193 (16%) transplant recipients who were tested for NoV had positive stool PCR. AKI occurred in 23% and persisted in 21% after 6 months. The median duration of diarrheal symptoms was 4 months (range, <1–20), and 11/31 (35.4%) of patients had relapsed after improvement. Wasting, incompatible kidney transplant status, and plasmapheresis were associated with longer diarrhea durations. Treatments included nitazoxanide (74%), reduction of immunosuppression (58%), and intravenous immunoglobulin (32%). Six patients died, but no deaths were attributed to NoV.
Gackler et al., 2[6]	2022	Germany	Prospective Cohort Study	The study included 60 renal transplant patients with NoV infection, 48% [29] had acute NoV infection only, and 52% [31] progressed to chronic NoV infection. In patients with chronic NoV infection, LOS was significantly prolonged (P = 0.024). Renal allograft function remained impaired in the chronic NoV group at 6 and 12 months after initial admission. Immunoglobulin therapy was administered to 18 patients with chronic NoV infection. No further clinical symptoms of NoV infection occurred in 13 (72%) of these patients. However, NoV was still detectable in stool specimens from 10 (77%) of these patients.
Brakemeier et al.,[7]	2016	Germany	Retrospective Cohort Study with case-control analysis	Sixty-five renal transplant patients with diarrhea had stool PCR-confirmed NoV infection, of these, 26 patients (40%) presented with AKI. In 43 patients (66.2%), dose reduction in immunosuppression was needed, and of 22 patients receiving tacrolimus, four patients (18.2%) had toxic levels above 15 ng/mL at the time of diagnosis. Ten patients (15.4%) developed chronic NoV infection. One-year patient and graft survival in patients and controls was 92.3% and 96.4%, respectively. Compared to controls, eGFR was already significantly lower before NoV infection and loss of eGFR relative to baseline over 12 and 36 months was significantly higher in NoV-infected patients.
Aulagnon F. et al.,[8]	2014	France	Retrospective Cohort Study with case-control analysis	NoV infection was diagnosed in 30% (59/195) of renal transplant patients with diarrhea. When compared with control, NoV patients had a greater weight loss, presented more frequently with acute renal failure (59 vs 38%, p = 0.006), consequently had a higher burden of diarrhea-related hospitalization, and experienced diarrhea for a longer period. Persisting symptoms led to a reduction of immunosuppressive drugs in 85% of the NoV patients. About 62% of NoV-infected patients demonstrated long-term viral shedding in stool.
Gras et al., 2 [9]	2021	France	Retrospective Cohort Study with case-control analysis	A total of 72 (7.3%) cases of NoV diarrhea were identified among 985 renal transplant cohorts. The median time between kidney transplantation and the diagnosis was 46.5 months. Following diagnosis, 93% of the cases had a reduction in immunosuppression. Acute rejection episodes were significantly more frequent among cases (13.8% versus 4.2% in controls; p = 0,03), but there was no difference in serum creatinine level at the last follow-up (p = 0.08).
Schorn et al., 2 [10]	2011	Germany	Case Series	The study included 9 kidney allograft recipients with chronic NoV with persistent virus shedding and intermittent diarrhea for a duration of 97–898 days. The intensity of immunosuppression correlated with diarrheal symptoms but not with viral shedding.

short and long-term outcomes [7–9]. In one study [7] the one-year graft survival in patients and controls was 92.3 % and 96.4 %, respectively [7]. Compared to controls, eGFR was already significantly lower before NoV infection, and loss of eGFR relative to baseline over 12 and 36 months was significantly higher in NoV-infected patients [7]. Another study [8] found that NoV patients had a more significant weight loss and presented more frequently with AKI compared with the control group (59 vs 38 %, $P = 0.006$), consequently, they had a higher burden of diarrhea-related hospitalization, and experienced diarrhea for a longer period [8].

The management involves initial resuscitation with aggressive rehydration, correction of electrolyte deficits, and optimization of renal function [10–13]. Adjusting immunosuppressive therapy is needed to avoid drug toxicity in the setting of reduced renal clearance, minimize further renal injury, and enhance the clearance of the virus by the immune system to alleviate the severity and duration of symptoms and possibly shorten viral shedding [7–13].

No specific antiviral drug is presently available [3]. Limited in-vivo studies have assessed the use of nitazoxanide (NTZ) for NoV infections in the transplant population [12], it is primarily an anti-helminthic and antiprotozoal thiazolide, but has been used for selected viral infections by activating the innate antiviral mechanisms and inhibiting certain cellular pathways that regulate viral replication [16]. A systematic review published in 2017 concluded that NTZ therapy may be useful to reduce the disease burden in transplant patients with viral gastroenteritis [17]. The Nitazoxanide for Norovirus in Transplant Patients Study (NNITS) is an ongoing phase 2 multicenter, double-blind, placebo-controlled study to determine the clinical and virologic efficacy and safety of NTZ for the treatment of symptomatic NoV diarrhea in solid organ transplant (SOT) and hematopoietic stem cell transplant (HSCT) populations (ClinicalTrials.gov Identifier: NCT03395405) [18]. Despite the clinical improvement with NTZ treatment, some patients continue to excrete the virus and stool PCR may remain positive for several months [19].

Human intravenous immunoglobulins (IVIs) therapy was also tried in small-sized cohorts [6]. IVIs therapy may be a promising option for chronic NoV in renal transplant recipients [6]. Nevertheless, the role, safety, and efficacy of IVIs deserve further elucidation in large-sized randomized trials.

Conclusion

The authors described a challenging case of persistent NoV infection in a young renal transplant patient that was associated with recurrent admissions with gross electrolyte disturbances, AKI, and significant weight loss. Chronic NoV infection has negatively impacted the patient's quality of life and socioeconomic performance. It has also posed a therapeutic challenge to the providers, as frequent adjustment of immunosuppressive medications was required in the setting of reduced renal clearance and the attempts to decrease immunosuppressive effects to enhance the virus clearing. The management of chronic NoV infections in the renal transplant population should involve a multidisciplinary team (including infectious disease, nephrology, and renal transplant, as well as social services) to achieve good outcomes for acute complications and minimize the adverse long-term physical and psychological impacts on the affected patients.

Learning points

- Norovirus (NoV) infections among patients with a renal transplant can present with severe acute and chronic diarrheal illnesses and may lead to adverse short-term outcomes (AKI and acute graft rejection) as well as long-term morbidities (persistent diarrhea and malabsorption syndrome, and reduced graft survival).
- The iatrogenic immunodeficiency status of renal transplant patients may result in persistent viral shedding due to impaired viral clearance.
- Extensive microbiology work-up is warranted in solid organ transplant (SOT) patients who present with relapsing or chronic diarrhea including stool PCR for *Norovirus* GI/GII, EPV serology, blood cultures for CMV, and stool acid-fast bacilli (AFP) stain for atypical mycobacterial (MAC) owing to iatrogenic cell-mediated immune suppression status of those patients.
- Frequent adjustment of immunosuppressive medications may be required in the setting of reduced renal clearance and the attempts to decrease immunosuppressive effects, with possible risks of acute graft rejection.
- No specific antiviral drugs are presently available, although trials of nitazoxanide are ongoing.
- The management of chronic relapsing NoV infections in renal transplant hosts should be multidisciplinary to achieve good outcomes, preserve graft function, and minimize adverse psychological and socioeconomic impacts on the affected patients.

Informed consent

Informed consent was obtained from the patient to write and publish her case as a case report with all accompanying clinical data. No personal identifying information has been used in this article.

CRediT authorship contribution statement

ES and MA contributed to conceptualizing. ES, MA, AA, MF, and AH contributed to writing the first manuscript. JS and HF performed the critical review and editing of the final draft. All authors agreed to the final draft submission.

Competing interests

The authors declare that they have no conflicts of interest regarding the publication of this case report.

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Authors statement

I would be happy to submit our manuscript entitled: " **Persistent *Norovirus* Infection in a Young Patient with Renal Transplant: The Challenging Cost of Immunosuppression and the Negative Impact on Patient's Quality of Life "** for submission to your journal for consideration for publication. I can confirm that all authors read the final draft and accepted it for submission. All authors have read and approved the submission of the article as it appears in the submission format.

I can also confirm that this manuscript has not been considered for submission to any other journals at this time of submission to the IDCases journal.

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