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CASE REPORT

# Norovirus gastroenteritis successfully treated with nitazoxanide

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## KEYWORDS

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**Summary** Infectious diarrhea is a common occurrence in the immunosuppressed population. We present a 43-year-old individual with large-volume stool output Norovirus acute gastroenteritis in the setting of relapsed refractory acute myelogenous leukemia, hematopoietic stem cell transplantation, and biopsy-proven cutaneous and pulmonary graft-versus-host disease. Therapeutic options such as intravenous immunoglobulin or reduction of immunosuppressants were not a feasible choice. A prompt clinical cure was achieved with nitazoxanide, a broad-spectrum antimicrobial agent. Nitazoxanide may be a safe therapeutic alternative, in which a reduction in immunosuppression may not be a viable option.

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## Case description

We present a 43-year-old Caucasian male with relapsed refractory acute myelogenous leukemia (AML) and an acute episode of Norovirus gastroenteritis (NoV). The patient initially started treatment for the AML with idarubicin and cytarabine. As he had relapsed, two years later he received a matched-related allogeneic hematopoietic stem cell transplant (HSCT). His post-transplant course was complicated with biopsy-proven chronic graft-versus-host disease (GVHD) of his skin and lungs. Eight years after the HSCT, he relapsed again. Therefore, as he was refractory to

conventional chemotherapy, he was initiated on an experimental agent, Ponatinib (an oral pan BCR-ABL tyrosine kinase inhibitor, ARIAD Pharmaceuticals).

Three months after initiating Ponatinib, the patient presented with a 10-day history of 8–12 daily episodes of large volume, non-dysenteric watery diarrhea. He denied having any fever, chills, or any associated abdominal pain or tenesmus. He had only consumed home-cooked food and bottled water. Of interest, prior to the patient's diarrheal illness, his 6-year-old kindergarten child had developed a self-limited 24-h course of watery diarrhea. His wife and daughter also developed a similar gastrointestinal

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illness, which self-resolved within 36-h. Throughout this period of time, the patient had been receiving tacrolimus 1 mg daily, methylprednisolone 12 mg twice daily and ciprofloxacin, voriconazole and valgacyclovir prophylaxis.

On admission, the patient was afebrile, but with a heart rate of 115, and a blood pressure of 85/55 mmHg. His physical exam was significant for chronic GVHD of his skin. His abdomen was non-tender but hyperactive. He had a white blood cell count of 8400 cells/ $\mu$ L, absolute neutrophil count of 0 cells/ $\mu$ L and absolute lymphocyte count of 480 cells/ $\mu$ L with 7890 circulating blast cells/ $\mu$ L. He had been severely neutropenic and lymphopenic for over the past 3 months. His hemoglobin was 9.4 g/dL, and platelets 18,000/ $\mu$ L. Serum cytomegalovirus (CMV) polymerase chain reaction (PCR) was negative. The patient was started empirically on cefpodoxime, metronidazole, loperamide and octreotide. Stool cultures were negative for *Salmonella* spp., *Shigella* spp., and *Campylobacter* spp. *Clostridium difficile* toxins A and B rapid immunoassay was negative on multiple occasions. Stool samples were also negative for *Cyclospora* spp., *Isospora* spp., *Microsporidium*, and *Cryptosporidium* spp. Based on the family's history of acute watery diarrhea, stool samples were sent for Rotavirus and Adenovirus antigen enzyme immunoassay (EIA), as well as Enterovirus culture and NoV reverse transcription (RT) PCR (Focus Diagnostics, Inc, Cypress, California). Only RT-PCR for NoV was positive.

A colonoscopy to rule out GVHD or CMV colitis was deferred, due to the fact that the patient was diagnosed with NoV gastroenteritis. Cefpodoxime and metronidazole were discontinued. Although, the patient received four days of octreotide and loperamide therapy, the patient's diarrhea persisted. A decrease in the dose of tacrolimus or methylprednisolone was not an option, due to the extent of the GVHD. Additionally, Intravenous immunoglobulin was contraindicated due to patient's prior history of anaphylactic shock. As a result, the patient was started on oral nitazoxanide 500 mg twice daily, given recent reports regarding this drug's anti-viral activity. Twenty-four hours after starting nitazoxanide, the frequency of his bowel movements declined from approximately 10, to 2 bowel movements per day. The consistency and frequency of his bowel movements returned to baseline within 4 days. Although, the patient had clinical resolution of his AGE with a 7-day course of nitazoxanide, he continued to asymptotically shed NoV in his stools for over 30 days.

## Discussion

In 1972, Kapikian et al. were the first to demonstrate the elusive 27 nm particle as the agent behind the non-bacterial acute gastroenteritis (AGE) outbreak in Norwalk, Ohio in the fall of 1968.<sup>1</sup> NoV is a non-enveloped, positive-sense, single-stranded RNA virus belonging to the Caliciviridae family.<sup>2</sup> The infectious dose of NoVs is near 49% for a single infectious virus particle, which is one of the highest reported for any viral infection.<sup>3</sup> Foodborne, person-to-person and contaminated environmental surfaces have all been described as routes of transmissions for NoV infection.<sup>4</sup> Outbreaks occur throughout the year, but over 80% of them occur during November to April.<sup>4</sup> The prevalence of NoV AGE in the US is approximately 23 million cases per year.<sup>5</sup> RT-PCR remains the gold standard for the diagnosis of NoV AGE.<sup>6</sup>

NoVs infection is characterized by a non-febrile, non-bloody watery diarrhea associated with vomiting, abdominal cramps, lasting for approximately 12–60 h. However, symptoms can last a median of 6 days in infants less than 1 year of age and 4 days in 40% of patients greater than 85 years of age.<sup>7,8</sup> Additionally, immunocompetent individuals have been observed to have asymptomatic viral shedding up to 3 weeks after the onset of clinical symptoms.<sup>7</sup> Immunocompromised individuals may shed the virus for an even longer duration of time, which may lead to further community and hospital outbreaks.<sup>9</sup>

Diarrhea is common in HSCT recipients, predominating within the first month after the HSCT.<sup>8</sup> Diarrhea occurs in approximately 47% of autologous and 79% of allogeneic HSCT recipients.<sup>10</sup> The early diarrheal episodes are most likely due to gastrointestinal (GI) mucosal toxicity secondary to the intense conditioning regimens, GI GVHD, and broad-spectrum antimicrobials.<sup>10</sup> *Clostridium difficile* is the most common bacterial agent isolated in approximately 4–30% of HSCT, mainly due to extensive hospitalizations and antimicrobial prophylaxis.<sup>10–12</sup> Viruses, such as NoV, CMV, Adenovirus, Rotavirus, Astrovirus and Coxsackie virus have all been responsible for causing diarrhea in the HSCT population.<sup>4,11–14</sup> The mortality rate among those infected appears to be significantly higher than those non-infected patients (55% vs. 13%,  $p < 0.001$ ).<sup>11</sup> Measures aimed at preventing and treating such infections might reduce the morbidity and mortality associated with HSCT.

To date, NoV AGE in immunosuppressed individuals, particularly the transplant population has not been widely reported. Roddie retrospectively reviewed 12 HSCT recipients with NoV AGE.<sup>15</sup> The median onset of diarrheal illness was 10.5 months post HSCT (ranging from 1 week to 14 months). The diarrheal illness lasted a median of 3 months for 10 patients (ranging from 2 weeks to 14 months). Similar to our patient, 4 individuals reported AGE outbreaks involving their family members. Eleven of the 12 patients were on immunosuppression and 9 were being treated for GVHD. RT-PCR was positive in all 12 cases, while only 2 out of 9 patients that had their stools tested with electron microscopy were positive. Treatment strategies included supportive care, as well as decreasing or stopping immunosuppression in 8 patients.<sup>15</sup>

Of interest, Blanco et al. described a patient with chronic NoV, with a double HSCT and GVHD-related bronchiolitis obliterans on immunosuppression with tacrolimus and mycophenolate. As sirolimus appears to have anti-viral activity, the calcineurin inhibitor was switched to sirolimus, a mammalian target of rapamycin inhibitor (mTOR-I). The patient's diarrhea resolved and fecal NoV RNA became undetectable. Therefore, mTOR-I may be considered as an alternative immunosuppressive agent in patients with GVHD and NoV infection.<sup>16</sup>

Nitazoxanide may also be another alternative for the treatment of NoV gastroenteritis. Nitazoxanide is an agent with broad antimicrobial activity (Table 1). In the 1970s, Rossignol synthesized this 5-nitrothiazole compound.<sup>17,18</sup> This drug is currently approved for Giardia and Cryptosporidium diarrhea in children and adults.<sup>19</sup> The direct inhibition of pyruvate-ferredoxin oxidoreductase reaction by nitazoxanide in the electron transport chain of protozoa and anaerobic bacteria could not explain the drug's anti-viral effect.<sup>19–21</sup>

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