While norovirus generally presents as a self-limited winter-time diarrheal illness, challenges arise in the workup and differential of persistent diarrhea in a patient without a functioning immune system. Persistent norovirus burden is a difficult to treat infection not uncommon to the immunocompromised patient population. Limited options exist for treatment, which include backwash of the immunosuppressive medications or thiazolides, a new class of broad spectrum antiviral medications.

Case

A 66 year old man with a past medical history of an orthotopic heart transplant two years prior for ischemic cardiomyopathy, taking mycophenolate and tacrolimus, in addition to hypertension, and diverticulosis presented to the hospital for the fourth time in six months with ongoing nausea, diarrhea, and abdominal pain without fever. He complains of daily episodes of loose watery stools, as many as 6 daily. With the loose stools, he also complains of diffuse, crampy abdominal pain, unrelated to eating, usually associated with his multiple loose stools. He feels constantly bloated, a symptom which seems to be getting worse, and is constantly nauseated, punctuated by the rare episode of emesis.

Prior to his admission, he had been seen by his PCP who worked him up with stool studies (stool culture for shigella, campylobacter, salmonella, E. coli 0157:H7, ova and parasites, cryptosporidium, giardia, HIV and fecal leukocytes). While these tests came back negative, a C. difficile EIA was positive and confirmed via PCR. He was treated as an outpatient with a course of oral metronidazole, however his symptoms persisted, ultimately bringing him to the emergency room shortly thereafter. He was admitted for dehydration in the setting of multiple episodes of diarrhea, with an inpatient workup including the same studies already sent by his PCP now demonstrating clearance of the C. difficile.

Additional workup at this time included a celiac panel, a colonoscopy with biopsy to rule out CMV, an EGD and a CT abdomen and pelvis, all of which were unremarkable. It was thought that this could be a side effect from his mycophenolate, and he was changed to a different formulation (myfortic) and discharged. A norovirus PCR at this time was pending, in addition to hypertension, and inpatient mycophenolate was reduced in dosage before discharge.

Norovirus infection has become an important consideration in the differential diagnosis of chronic diarrhea, notably in patients without a functional immune system. It may be the cause of gastroenteritis in as many as one fourth of patients of this population presenting with diarrhea, although their presentation is often markedly different, as shown in this case.

A) Duodenal biopsy 4 weeks after acute norovirus infection (broadened and shortened villi) in a patient on tacrolimus from a kidney transplant
B) CD8+ intraepithelial T-cells in the upper-normal range at 34/100
C) Duodenal biopsy 2 months later showing persistent partial villous atrophy after repeated episodes of diarrhea
D) Increase in CD8+ T-cells now abnormally high at 61/100

Introduction

While norovirus generally presents as a self-limited winter-time diarrheal illness, challenges arise in the workup and differential of persistent diarrhea in a patient without a functioning immune system. Persistent norovirus burden is a difficult to treat infection not uncommon to the immunocompromised patient population. Limited options exist for treatment, which include backwash of the immunosuppressive medications or thiazolides, a new class of broad spectrum antiviral medications.

Discussion

Disease burden from norovirus in the immunosuppressed patient is difficult to treat as generally the cell-mediated immunity required to fight an acute gastrointestinal virus are the same cells being suppressed to stave off graft rejection. This was shown in renal transplant patients (below) with acute norovirus, with duodenal biopsies showing a normal amount of cytotoxic T-cells, which ultimately led to a chronic infection.

While not shown to have a benefit in chronic norovirus infections, nitazoxamide was given to our patient. At a six week follow up, the patient remains asymptomatic and serum PCR has demonstrated viral clearance.

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Treatment options are often very limited in these patients, especially when holding or stopping immunosuppression is not an option. In our patient, who was two years out from a heart transplant, holding tacrolimus and mycophenolate was not possible. With our patient already symptomatic for months, it was clear that he needed to be hospitalized twice, another solution had to be synthesized. One relatively new development has been the use of nitazoxamide, a thiazolide class of antiviral drug which has been studied for treatment of norovirus gastroenteritis. Currently, nitazoxamide’s mechanism of action against the virus is not entirely clear. It functions by directly inhibiting pyruvate-ferredoxin oxidoreductase in protozoa and anaerobic bacteria, however this does not explain it’s anti-viral effect. In one study of placebo versus this medication for acute norovirus gastroenteritis, a decrease in length of infection was shown:

References