A 56-year-old man presented with a 3-week history of copious, watery, and foul-smelling diarrhea as well as very mild abdominal cramping, nonbilious vomiting, and a 25-lb weight loss. The patient had a history of familial glomerosclerosis, which required renal transplantation 3 years earlier. His symptoms were unaffected by changes in diet. He noticed mucus in his stools, which appeared like flecks of tissue paper. He denied odynophagia, hematochezia, melena, pain with defecation, fever, or night sweats. The patient reported frequent travel to Europe in the 6 weeks before the onset of symptoms. He denied smoking, alcohol, or illicit drug use. His daily medications included mycophenolate mofetil, tacrolimus, prednisone, and amlodipine.

Physical examination revealed a temperature of 36.6°C, a heart rate of 71 beats/min, and a blood pressure of 90/63 mm Hg. The patient was breathing comfortably on room air with a respiration rate of 18 breaths/min. His heart rhythm was regular, and his lungs were clear bilaterally. No peripheral edema was found. The abdomen was soft, nondistended, and nontender, with normal bowel sounds.

Laboratory data included the following (references ranges provided parenthetically): hemoglobin level, 16.2 g/dL (13.2-16.6 g/dL); white blood cell count, 4.7×10⁹/L ((3.4-9.6)×10⁹/L); platelet count, 201×10⁹/L ((135-317)×10⁹/L); sodium level, 133 mmol/L (135-145 mmol/L); potassium level, 3.0 mmol/L (3.6-5.2 mmol/L); chloride level, 104 mmol/L (98-107 mmol/L); HCO₃ level, 11 mmol/L (22-29 mmol/L); blood urea nitrogen level, 107 mg/dL (8-24 mg/dL); creatinine level, 5.75 mg/dL (0.74-1.35 mg/dL); glucose level, 119 mg/dL (70-140 mg/dL); international normalized ratio, 1.12 (0.9-1.1); albumin level, 3.6 g/dL (3.5-5.0 g/dL); and total protein level, 6.0 g/dL (6.3-7.9 g/dL).

Computed tomography of the abdomen and pelvis with intravenous (IV) contrast revealed a right lower quadrant renal transplant without hydronephrosis or other abnormalities.

1. Which one of the following was the most likely cause of the patient's initial clinical manifestations?
   a. Ulcerative colitis
   b. Intestinal ischemia
   c. Infectious diarrhea
   d. Celiac disease
   e. Carcinoid syndrome

Our patient had no history of inflammatory bowel disease, and de novo ulcerative colitis without bleeding would be unlikely, especially in someone who was already taking immunosuppressants. Intestinal ischemia is caused by processes that reduce intestinal blood flow such as atherosclerosis and usually presents with severe abdominal pain. The absence of vascular disease or major cardiovascular risk factors in a patient with minimal abdominal discomfort does not support the diagnosis of ischemia. Given the new-onset, high-volume diarrhea, vomiting, and history of recent travel, the most likely etiology was infectious diarrhea. Diarrheal episodes are common after solid organ transplantation and may be caused by various organisms. Organ recipients are at high risk for infectious causes of diarrhea because of daily antirejection medications.

Celiac disease may cause chronic, large-volume diarrhea, and weight loss, but this is less likely given the acuteness of the patient's symptoms and the lack of history of gluten intolerance. Carcinoid syndrome is unlikely, as the patient did not exhibit cutaneous flushing or wheezing along with diarrhea.

The patient was treated with IV fluids and his creatinine level improved, indicating severe prerenal injury from volume depletion.
Stool studies including bacterial cultures and viral polymerase chain reaction panel was negative. The serum cytomegalovirus serologic test result was also negative. The stool ova and parasite study was positive for Cryptosporidium.

2. Which one of the following was the most appropriate antibiotic treatment for our patient?
   a. Metronidazole
   b. Nitazoxanide
   c. Ciprofloxacin
   d. Albendazole
   e. Trimethoprim/sulfamethoxazole

Metronidazole is an antimicrobial within the nitroimidazole class, typically used in the treatment of mild to moderate cases of Clostridium difficile as well as protozoal infections such as giardiasis. Nitazoxanide, a thiazole compound with broad activity against bacteria, viruses, and parasites, is currently the only Food and Drug Administration–approved drug for the treatment of cryptosporidiosis.1

The recommended treatment length is 2 weeks, but may be prolonged to 4 to 6 weeks in immunocompromised patients.

Ciprofloxacin is a fluoroquinolone commonly used to treat bacterial causes of diarrhea such as Escherichia coli and Shigella. Albendazole is an antiparasitic medication used in the treatment of various worm infections including microsporidiosis. Trimethoprim/sulfamethoxazole is used to treat Cyclospora or Isospora. None of the aforementioned agents with the exception of nitazoxanide are efficacious against Cryptosporidium.

Our patient was treated with nitazoxanide 500 mg twice daily; however, he continued to have large-volume diarrhea (4-8 L/d). As other infectious stool studies were negative, he was treated with loperamide and atropine/diphenoxylate as well as azithromycin 500 mg daily but the stool output remained unchanged.

3. Which one of the following was the next best step in the patient’s care?
   a. Computed tomography enterography
   b. Colonoscopy
   c. Supportive therapy and observation
   d. Abdominal ultrasound
   e. Hydrogen breath test

Computed tomography enterography is often used to diagnose small bowel neoplasms, unlikely the cause of our patient’s diarrhea given its acute nature. In our immunocompromised patient with persistent diarrhea despite treatment, colonoscopy with biopsies should be performed to rule out cytomegalovirus, Mycobacterial avium complex, and other forms of inflammatory colitis. Supportive therapy is essential, but further work-up should be pursued in an immunocompromised patient with severe diarrhea who fails to improve with appropriate therapy. Abdominal ultrasonography is valuable in the evaluation of hepatic, biliary, and pancreatic pathology, but would not be diagnostically useful in our patient’s case as he has no signs of organ dysfunction in these systems. A hydrogen breath test is used to diagnose small intestinal bacterial overgrowth, a cause of chronic diarrhea. Small intestinal bacterial overgrowth is typically associated with intestinal motility disorders, diabetes, and previous small bowel surgery, none of which were part of our patient’s medical history. Therefore, a hydrogen breath test would not be useful at this time.

Esophagogastroduodenoscopy and colonoscopy revealed nonbleeding erosive ulcers in the gastric body and diffusely granular mucosa in the transverse colon. Biopsies revealed evidence of colitis with intraluminal microorganisms consistent with Cryptosporidium and mild patchy crypt apoptosis. No granulomas or viral-type inclusions were seen. Congo red staining exhibited no evidence of amyloid.

4. Which one of the following medications on the patient’s medication list most likely contributed to the patient’s persistent diarrhea?
   a. Prednisone
   b. Nitazoxanide
   c. Amlodipine
   d. Mycophenolate mofetil
   e. Tacrolimus
Prednisone has no known association with diarrhea and is often used to treat diarrhea due to inflammatory causes. Nitazoxanide may cause abdominal pain and nausea, but not diarrhea. Amlodipine is known to cause constipation more commonly than diarrhea. The finding of crypt apoptosis on histology is most often associated with mycophenolate mofetil–induced colitis. Among the immunosuppressive agents used in solid organ transplantation, mycophenolate mofetil is also most frequently associated with persistent diarrhea. Tacrolimus has been associated with mild diarrhea and abdominal discomfort, but is not known to cause changes in the intestinal mucosa.

Mycophenolate mofetil was discontinued, and over the next few days, the patient’s stool output improved to approximately 1 L/d. He continued to receive IV fluids to match stool output, and his creatinine level returned to baseline. However, he exhibited worsening edema progressing to anasarca. His serum albumin and total protein levels decreased slowly throughout the hospitalization, with the albumin level reaching a nadir of 1.9 g/dL (RR, 3.5-5.0 g/dL) and the total protein level 3.6 g/dL (RR, 6.3-7.9 g/dL). He had a good caloric intake, and no proteinuria was seen on urine studies.

5. Which one of the following laboratory tests would be most useful in diagnosing the cause of the patient’s hypoalbuminemia?

a. Fecal lactoferrin
b. Fecal calprotectin
c. Fecal fat
d. Fecal reducing substances
e. Fecal alpha-1 antitrypsin (A1AT)

Fecal lactoferrin and calprotectin are markers of inflammation that are often elevated in severe gastrointestinal infections and disease such as inflammatory bowel disease. However, inflammatory bowel disease was unlikely given the absence of suggestive findings on biopsy. Levels of fecal fat are increased in the stool in malabsorptive conditions such as pancreatic insufficiency, celiac disease, and small intestinal bacterial overgrowth. Fecal reducing substances are used to diagnose lactose deficiency and other causes of disaccharidase deficiencies. Neither test would fully explain the low levels of serum protein and albumin.

Alpha-1 antitrypsin intestinal clearance is the primary test to diagnose protein-losing enteropathy, which was clinically suspected given the patient’s gradual hypoalbuminemia, hypoproteinemia, edema, and lack of proteinuria. Alpha-1 antitrypsin has high molecular weight, is minimally degraded in the gut, and is excreted in an intact form. Its clearance is calculated by 24-hour stool collection and comparison to the serum values.

Stool collection indicated elevated A1AT clearance, confirming the diagnosis of protein-losing enteropathy, and a low-fat, high-protein, medium-chain triglyceride diet was initiated. The patient continued to improve and, at the time of discharge, had only 1 to 2 episodes of diarrhea daily and no abdominal pain or other symptoms. Nitazoxanide and azithromycin were continued for 8 weeks given the patient’s diffuse intestinal disease and immunosuppressed state.

At follow-up in the outpatient clinic after the completion of the antibiotic course, the patient’s symptoms had fully resolved.

DISCUSSION

Diarrhea is a frequent complication after solid organ transplantation, with approximately 20% of patients having it in the first 3 years. Compared with the nontransplanted population, there is a higher likelihood of opportunistic infections and rare causes of diarrhea. The most common infectious pathogens are Norovirus and C. difficile. However, other common pathogens include Cytomegalovirus, Salmonella, and parasites such as Cryptosporidium as seen in our patient.

Within the Cryptosporidium genus, Cryptosporidium parvum is the most common species that affects humans. It has a ubiquitous geographical distribution and wide host range. Cryptospora typically spread in outbreaks of waterborne infections, with as few as 30 microscopic oocysts possibly leading to infection. Cryptosporidiosis accounts for up to 6% of all diarrheal diseases in immunocompetent individuals and up to...
24% cases in those with AIDS; however, its incidence is unknown in those with solid organ transplant. In healthy individuals, cryptosporidiosis is typically self-limiting, but it may be life-threatening in the immunocompromised who has copious diarrhea with subsequent volume depletion, electrolyte abnormalities, acute kidney injury, and fluctuating levels of antirejection drugs. Other clinical manifestations include nausea and/or vomiting, fever, and abdominal pain.

The mainstay of treatment of cryptosporidiosis is supportive therapy through oral and IV volume repletion, but antidiarrheal agents may be used after other infectious causes have been excluded. To date, there are no randomized clinical trials of the efficacy of antiparasitic drugs in the treatment of cryptosporidiosis in solid organ transplant recipients. Most current data are extrapolated from studies of immunocompetent hosts or patients with human immunodeficiency virus infection. Nitazoxanide, a thiazole compound with broad activity against bacteria, viruses, and parasites, is currently the only Food and Drug Administration–approved drug for the treatment of cryptosporidiosis. In immunocompromised hosts, antimicrobial therapy is administered for 2 weeks or longer, depending on the clinical response. In patients with more severe disease and minimal response to a single agent, combination therapy and a longer duration of treatment may be considered. Nitazoxanide in combination with azithromycin has been found to significantly suppress the growth of Cryptosporidium in vitro. This regimen used for 4 to 6 weeks resulted in clinical improvement and eradication of the parasite in a case series of patients with renal and hematopoietic cell transplant.

Noninfectious causes must also be considered in patients with solid organ transplant, with the most common being drug-induced, particularly considering that most immunosuppressive therapies used in antitransplant rejection are associated with diarrhea. Tacrolimus and azathioprine are known to cause gut irritation; however, gastrointestinal adverse effects associated with these medications are typically mild and rarely require drug discontinuation. The highest incidence of diarrhea related to antirejection medication is associated with mycophenolate mofetil, which is believed to cause direct enterocyte damage. Characteristic histological features of mycophenolate mofetil enteritis include crypt apoptosis, presence of apoptotic bodies, and lymphoplasmacytic infiltrates, some of which were seen in our patient’s biopsy. Treatment involves cessation of the drug, after which swift clinical improvement is often seen.

Lastly, throughout hospitalization, our patient had protein-losing enteropathy leading to hypoalbuminemia and edema. There have been case reports of protein-losing enteropathies associated with C. difficile infections, as well as parasitic infections such as Giardia lamblia and Strongyloides stercoralis. Severe infections may cause erosive gastrointestinal disease, leading to leakage of protein-rich fluids across the eroded epithelium. Diagnosis can be confirmed via measurement of A1AT levels in the stool. Management involves treatment of the underlying cause with initial dietary adjustments using a high-protein, low-fat, medium-chain triglyceride diet. These dietary modifications may beneficially affect albumin metabolism and diminish the need for lymphatic transport of fatty acids, thus decreasing pressure on the lymphatic system and preventing lymph leakage.

Potential Competing Interests: The authors report no competing interests.

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REFERENCES

CORRECT ANSWERS: 1. c. 2. b. 3. b. 4. d. 5. e.