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Zinc Level and Its Role in Recurrent *Clostridium difficile* Infection: A Case Report and Literature Review

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Abstract

Clostridium difficile infection is a common nosocomial infection in US hospitals, accounting for approximately 12 800 deaths annually in the United States. These infections are often associated with the use of antibiotics, which can alter the gut microbiome and thus render patients susceptible to *C difficile* infection. *C difficile* is often spread via fecal oral transmission. Multiple medications have been developed, but recurrence rates reach 60% after treatment. Recent data have shown that zinc supplementation decreases the recurrence of *C difficile* infection. In this article, we present a case of recurrent *C difficile* infection with zinc deficiency in which zinc supplementation improved the symptoms and reduced the incidence of recurrence.

Keywords

recurrent *Clostridium difficile* infection, zinc supplementation, zinc deficiency

Introduction

Clostridium difficile infection is a common cause of nosocomial infections in US hospitals and is the ninth leading cause of death related to gastrointestinal diseases.[1] According to the Centers of Disease Control and Prevention, approximately 2.8 million antibiotic-resistant infections occur annually in the United States, and in 2017, 223 900 cases of *C difficile* infections were reported, from which 12 800 people died.[2] *C difficile* infection results from increased exposure to antibiotics, which alter the natural flora of the intestine. A meta-analysis reported that *C difficile* infection is most strongly associated with such antibiotics as third-generation cephalosporins, clindamycin, carbapenems, trimethoprim/sulfonamides, and fluoroquinolones.[3] In addition to antibiotics, proton pump inhibitors have also played a role in causing *C difficile* colitis. Infection risk was very high within the first month but can remain high for up to 3 months after antibiotic exposure, and the recurrence rate is 20.9% after initial infection; thereafter, the risk of multiple recurrent infections is higher.[4-6] Multiple treatment options, such as metronidazole, vancomycin, nitazoxanide, fidaxomicin, and fecal microbiota transplantation (FMT), have been developed for the treatment of initial and recurrent *C difficile* infection. Recent emerging data have indicated that zinc deficiency is associated with an increased recurrence of *C difficile* infection. Zinc is an essential trace element obtained from the diet and is excreted via the gastrointestinal tract. The World Health Organization recommends zinc supplementation in the treatment of acute diarrheal illness.[7] In this article, we present an interesting case of recurrent *C difficile* infection with zinc deficiency, in which zinc supplementation improved the symptoms and reduced the incidence of recurrence.

Case Report

A 52-year-old male with a previous medical history of type 1 diabetes mellitus, s/p renal transplant on tacrolimus and prednisone, recurrent *C difficile* infection, legal blindness, and left below-knee amputation presented to the emergency department in January 2020 for weakness. On admission, the patient was hypotensive with a systolic blood pressure of 90 mm Hg and acidotic with a bicarbonate level of 12 mEq/L; additionally, he presented with an anion gap of 24 mmol/L, an elevated blood sugar level of 481 mg/dL, a creatinine level of 4.5 mg/dL, and a baseline creatinine of 2.2 mg/dL. The patient was admitted to an intensive care unit under the impression of hypovolemia and diabetic ketoacidosis. The

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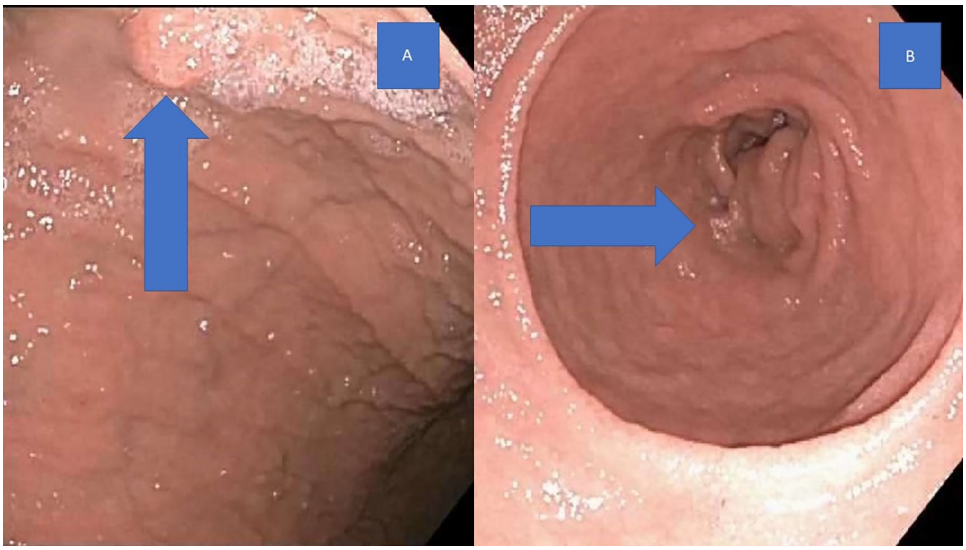

Figure 1. Gastric polyp (shown by arrow; A). Normal pylorus (shown by arrow; B).

patient was started on intravenous fluids and an insulin drip and exhibited improvements within 48 hours. His vital signs were stable, with a systolic blood pressure >110 mm Hg, a bicarbonate level of 20 mEq/L, a closed anion gap, and normal sugar level. The insulin drip was then switched to long-acting Lantus. During this admission, the patient had diarrhea and was tested positive for *C difficile* infection, with no recent history of antibiotic use. As noted above, the patient had a history of recurrent *C difficile* infection.

The patient experienced his first episode of *C difficile* infection in July 2019 and was treated with vancomycin for 14 days. At the time of this episode, he reported a history of antibiotic use (cefdinir) for a urinary tract infection. After completing the vancomycin course later in September 2019, the patient returned to the hospital with complaints of diarrhea and tested positive for *C difficile*. At this time, the patient was treated with another long taper of vancomycin. He again returned with similar complaints in January 2020 (the current admission) with recurrent *C difficile* infection. During the intervals between episodes, the patient never reported a complete relief of diarrhea and reported a weight loss of 30 lbs.

During this admission, given his weight loss, the patient underwent endoscopy and colonoscopy, the results of which were normal (Figures 1 and 2). Random biopsies in the duodenum and stomach revealed mild reactive epithelial changes, and random colon biopsies were normal. Given his nutritional status, his zinc levels were assessed and found to be low, at 36 µg/dL (60-130 µg/dL). The patient refused FMT during this admission; thus, he was treated with long-taper vancomycin and zinc supplementation. The patient improved and was discharged to rehabilitation in a stable condition. The patient received follow-up care in the clinic and reported a relief of symptoms, including diarrhea, after completion of the *C difficile* treatment, and subsequently, the patient continued to receive zinc supplementation. The patient has not had any further episodes of *C difficile* infection within the past 3 months.

Discussion

Clostridium difficile is a Gram-positive anaerobic spore-forming bacterium that produces enterotoxins. *C difficile* was first described by Hall and O'Toole in 1935 based on their investigation of bacterial flora in newborns. In 1978, *C difficile* was isolated in the stool of a pseudomembranous colitis patient.[8,9] *C difficile* produces 2 toxins: toxin A (enterotoxin) and toxin B (cytotoxin). These toxins are glucosyltransferases that inactivate the small GTP-binding protein Rho, which leads to disruption of the cytoskeleton. These toxins exhibit synergistic action with other pro-inflammatory mediators and cytokines and result in inflammation, injury, and cell death.[10] In addition to the major toxins, other toxins such as CDT binary toxin, fibronectin-binding protein FbpA, fimbriae, SlpA S-layer, Cwp84 cysteine protease, and Cwp66 and CwpV adhesions are also known to cause inflammation and intestinal injury.[11] The gut microbiota generally prevents the colonization of *C difficile* bacteria; however, when the gut flora is disrupted by antibiotic use, bacteria colonization and infection can result. *C difficile* is spread through fecal oral transmission via spore formation. The resultant intestinal injury and inflammation lead to varied symptoms, ranging from mild symptoms such as abdominal pain, nausea, vomiting, diarrhea, and melena to severe symptoms such as severe dehydration, hypovolemia and hypoalbuminemia, megacolon, ileus, perforation, and death. This condition also causes deficiencies in trace

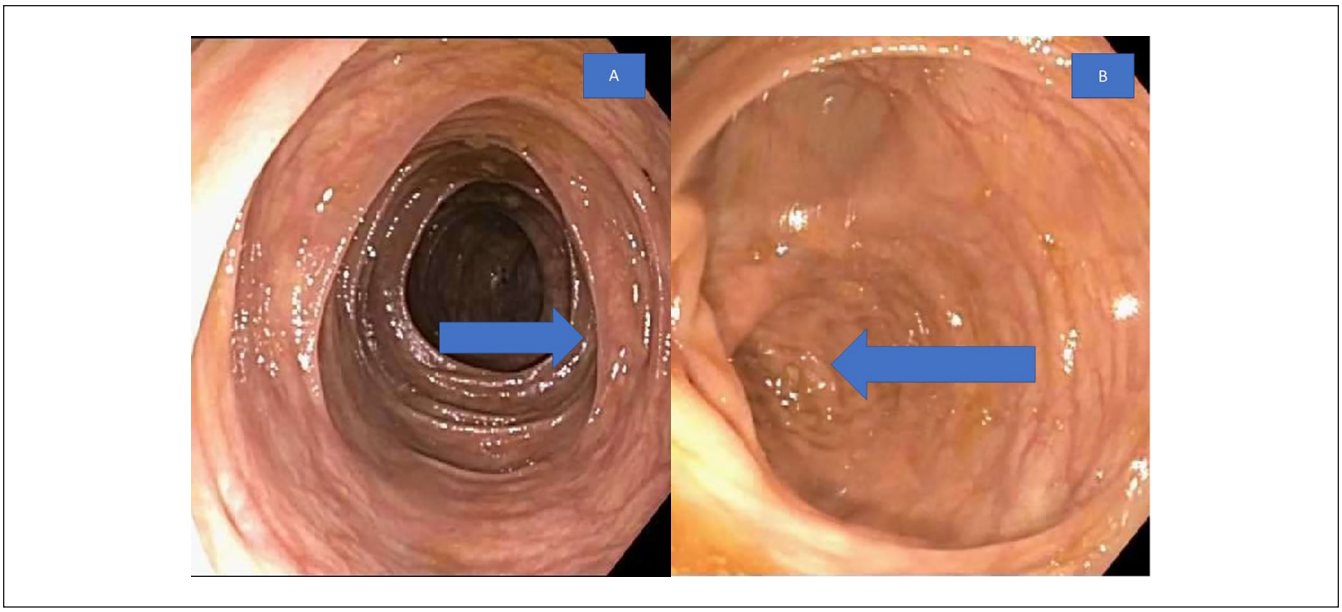

Figure 2. Normal colonic mucosa (shown by arrow; A). Normal ileocecal valve (shown by arrow; B).

elements secondary to impaired intestinal absorption and increased losses.[12]

Zinc is an essential trace element that plays a vital role in maintaining various physiologic and metabolic processes, such as immune functioning, protein synthesis, and DNA synthesis, thus supporting normal growth and development. Zinc also exhibits antioxidant properties, facilitating wound healing.[13] In previous works, zinc deficiencies have been well-documented in celiac disease, ulcerative colitis, and Crohn's disease secondary to malabsorption and inflammation of the intestinal wall.[14] Diarrhea caused by zinc deficiency has been reported in infants with hereditary acrodermatitis enteropathica and in adults with total parenteral nutrition.[15,16] It is thought that zinc deficiency increases activation of the nitric oxide synthase pathway and intestinal uroguanylin, both of which alter intestinal permeability and thus cause diarrhea.[17] This interpretation has been supported by a meta-analysis demonstrating that zinc supplementation reduces the incidence of diarrhea in children.[18] In addition, zinc can influence the microbiome in the gut; for example, multiple studies in pigs have reported that high levels of zinc oxide regulate the ileum microbiome in piglets.[19,20]

The 2 above-mentioned studies support our observation that zinc deficiency caused our patient to experience multiple recurrent *C difficile* infections and that zinc supplementation improved his symptoms and reduced the recurrence of *C difficile*. In a retrospective cohort study published in 2018, the authors studied the relationship between zinc deficiency and *C difficile* recurrence after FMT treatment.[21] A total of 80 patients were included in this study, 31 patients with low zinc levels and 59 patients with normal zinc levels. Five of the 31 low-zinc patients (16%) experienced recurrent *C difficile* infections compared with 3 of the 49 (6%) normal-zinc patients. After the patients in the low-zinc group were treated with zinc supplementation, the rate of *C difficile* infection decreased to 8% compared with 50% among patients who did not receive supplementation. This study supports prior evidence indicating that zinc deficiency plays an important role in the recurrence of *C difficile* infection. In contrast, one study in mice found that a high-zinc diet rendered mice susceptible to severe *C difficile* infection, while normal zinc supplementation had no effect on *C difficile* infection.[22] In addition, it seems that zinc supplementation should only be considered in zinc-deficient individuals, particularly in light of conflicting reports regarding the impact of zinc supplementation on the pathogenesis of *C difficile*, and in the future studies are necessary to clearly determine the role of zinc in reducing *C difficile* recurrence rates.

Authors' Note

Any enquiries regarding supporting data availability of this study should be directed to the corresponding author.

Author Contributions

Article guarantor, literature research, and manuscript preparation: Swetha Parvataneni

Case management, manuscript editing, manuscript revision/review, and final version approval: Swetha Parvataneni and Avinash R. Dasari

Declaration of Conflicting Interests

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Ethics Approval

Our institution does not require ethics approval for reporting individual cases.

Informed consent

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