Clostridioides difficile Infection following Procalcitonin-guided Antibiotic Therapy for COVID-19

Anton G. Elepaño, MD, Jonnel B. Poblete, MD, A. Nico Nahar I. Pajes, MD and Aldrin B. Loyola, MD

Philippine General Hospital, University of the Philippines Manila

ABSTRACT

We present a case of a 50-year-old man with chronic kidney disease (CKD) presenting with acute diarrhea and fever. He was admitted a month prior for COVID-19, where he received antibiotics for radiographic findings of pneumonia and elevated procalcitonin. In the emergency department, his stool sample tested positive for *Clostridioides difficile* antigen and toxin. He was given oral vancomycin and intravenous metronidazole for fulminant *C. difficile* infection and was discharged with resolution of symptoms. This case documents a potential risk associated with routine antibiotic use during the pandemic and the pitfalls in interpreting procalcitonin, especially in patients with COVID-19 and CKD.

Keywords: COVID-19, Clostridioides difficile, antibiotic-associated colitis

INTRODUCTION

Fulminant *Clostridioides difficile* infection (CDI) is a potential complication of antibiotic therapy, which carries a high mortality rate. Among patients with COVID-19, the use of antibiotics has been reported to be as high as 75%.[1] Philippine clinical guideline recommends against routine antibiotic therapy among critically ill patients with COVID-19 unless suspected of bacterial coinfection.[2,3] Clinically, it may be challenging to differentiate between the signs and symptoms of bacterial pneumonia and COVID-19.

Procalcitonin, a propeptide of calcitonin expressed by thyroid C-cells in response to bacterial infection, has been used to guide antibiotic discontinuation in patients with respiratory infections pre-pandemic. Meanwhile, local COVID-19 guidelines have recommended against its use as a basis for initiation of antibiotics, and the available evidence on its use showed low sensitivity in detecting community-acquired pneumonia among patients with COVID-19.[3,4]

Antibiotic stewardship during the pandemic remains important as the various side effects of these drugs may often be overlooked. This case report examines one such risk associated with routine antibiotic therapy—*C. difficile* infection.

CASE

A 50-year-old retired carpenter, who had a history of osteoarthritis and was on chronic hemodialysis for analgesic-related CKD, consulted the emergency room for diarrhea. He was admitted one month prior for moderate COVID-19 presenting with fever and anosmia without cough. At that time, he was given ceftriaxone and azithromycin for findings

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Corresponding author: Anton G. Elepaño, MD
Philippine General Hospital
University of the Philippines Manila
Taft Avenue, Ermita, Manila 1000, Philippines
Email: agelepano@up.edu.ph
ORCiD: https://orcid.org/0000-0002-8709-135X

of pneumonia on chest radiograph (Figure 1). Blood cultures extracted before antibiotic treatment came back negative. The patient was unable to expectorate for sputum gram stain and culture. Procalcitonin on admission was elevated (7.0 ng/mL), prompting the continuation of antibiotics. A repeat procalcitonin taken on day three of antibiotics and 24 hours post-hemodialysis showed an interval decrease by 71% (2.0 ng/mL) from baseline. The patient completed seven days of empiric antibiotics and was discharged well. One month after hospital discharge, he developed fever (38.0°C), crampy lower abdominal pain, and non-bloody mucoid loose yellow stools occurring six times per day. This has led him to miss scheduled sessions of dialysis. The symptoms persisted for one week prompting readmission to the same institution.

Upon examination at the emergency department, he was alert and coherent with elevated blood pressure (135/87 mmHg), tachycardia (120 bpm), and no fever (36.0°C). His abdomen was soft with dullness and tenderness over bilateral lower quadrants without guarding. He had an arteriovenous fistula on the left arm used for hemodialysis. The rest of the physical examination was unremarkable.

METHODS

A diarrheal stool sample was tested using Immunocard® (Meridian Bioscience) enzyme immunoassay and returned positive for *C. difficile* antigen (glutamate dehydrogenase), toxin A, and toxin B. There were innumerable fecal leukocytes without blood or parasite ova on fecalysis. The initial white blood cell count was elevated (38.2 x 10^9 cells/L), stratifying the patient to have severe CDI. The rest of the full blood count showed anemia (88 g/L), neutrophilia (35.1 x 10^9 cells/L), lymphopenia (1.1 x 10^9 cells/L), and thrombocytosis (474 x 10^9 cells/L). Subsequent abdominal computed tomography with oral, rectal, and intravenous contrast was requested when the patient developed hypotension (Figure 2). This revealed pancolitis with no signs of bowel perforation. A nasopharyngeal swab sent for SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) was negative. The stool culture did not grow any enteric pathogens. Blood cultures came back negative. Pertinent findings on blood chemistry were elevated creatinine (1859 µmol/L) and hyperkalemia (7.3 mmol/L).

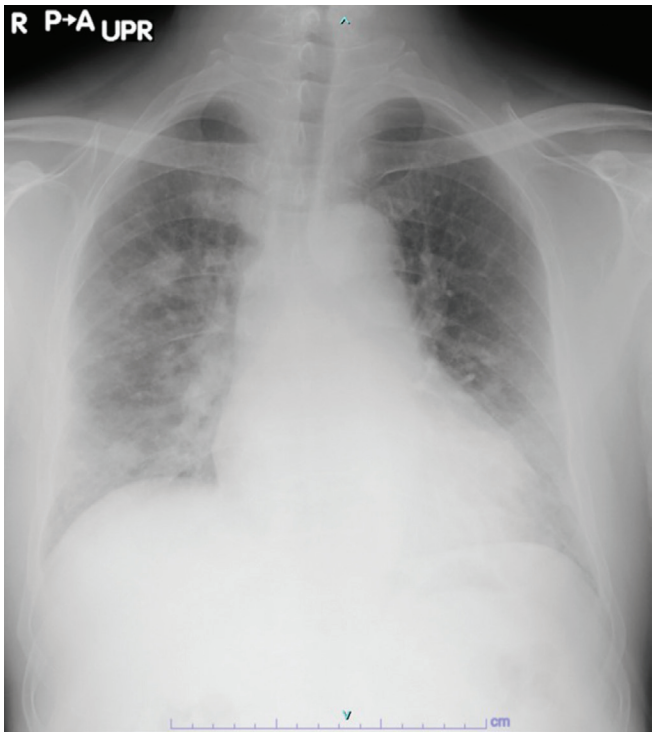

Figure 1. Chest radiograph showed patchy airspace and ground glass opacities in the bilateral middle to lower lung zones consistent with pneumonia.

Treatment and Outcome

The stool *C. difficile* antigen and toxin assays came back positive within six hours from the patient's admission. He was given oral vancomycin 125 mg every six hours using the following reconstitution method: 500 mg of powdered vancomycin was initially diluted in 10 mL of sterile water. From this solution, 2.5 mL was taken and added to 30 mL of flavored drink to improve the palatability of each dose. However, during hemodialysis, the patient developed episodes of hypotension necessitating low-dose norepinephrine despite an ultrafiltration volume of 0 L. The patient was assessed to have no new symptoms. Physical exam showed non-distended neck veins, clear breath sounds, and warm extremities. A chest radiograph done was unremarkable. Given that there was no other identifiable cause of the hypotension besides infection, he was restratified to have fulminant CDI. Oral vancomycin dosing was revised to 500 mg four times a day using the same formulation, and intravenous metronidazole 500 mg every eight hours was added.

After three days of receiving oral vancomycin, the patient had defervescence, improved white blood cell count (9.6 from a baseline of 38.2 x 10^9 cells/L), decreased frequency of loose stools (twice per day), and no recurrence of intra-dialytic hypotension. He was eventually able to complete ten days of the antibiotics without in-hospital complications. Upon discharge, he had semi-formed stools and was normokalemic (4.4 mmol/L). On follow-up one month after discharge, the patient reported being able to do household work independently, and there were no subsequent episodes of diarrhea.

DISCUSSION

Antibiotic use is a known risk factor for CDI. Intestinal microbiota diversity and overall size are both decreased following antibiotic treatment. This sets an ideal environment for *C. difficile* to invade intestinal mucosa and facilitate spore germination.[5] The available literature on the incidence of

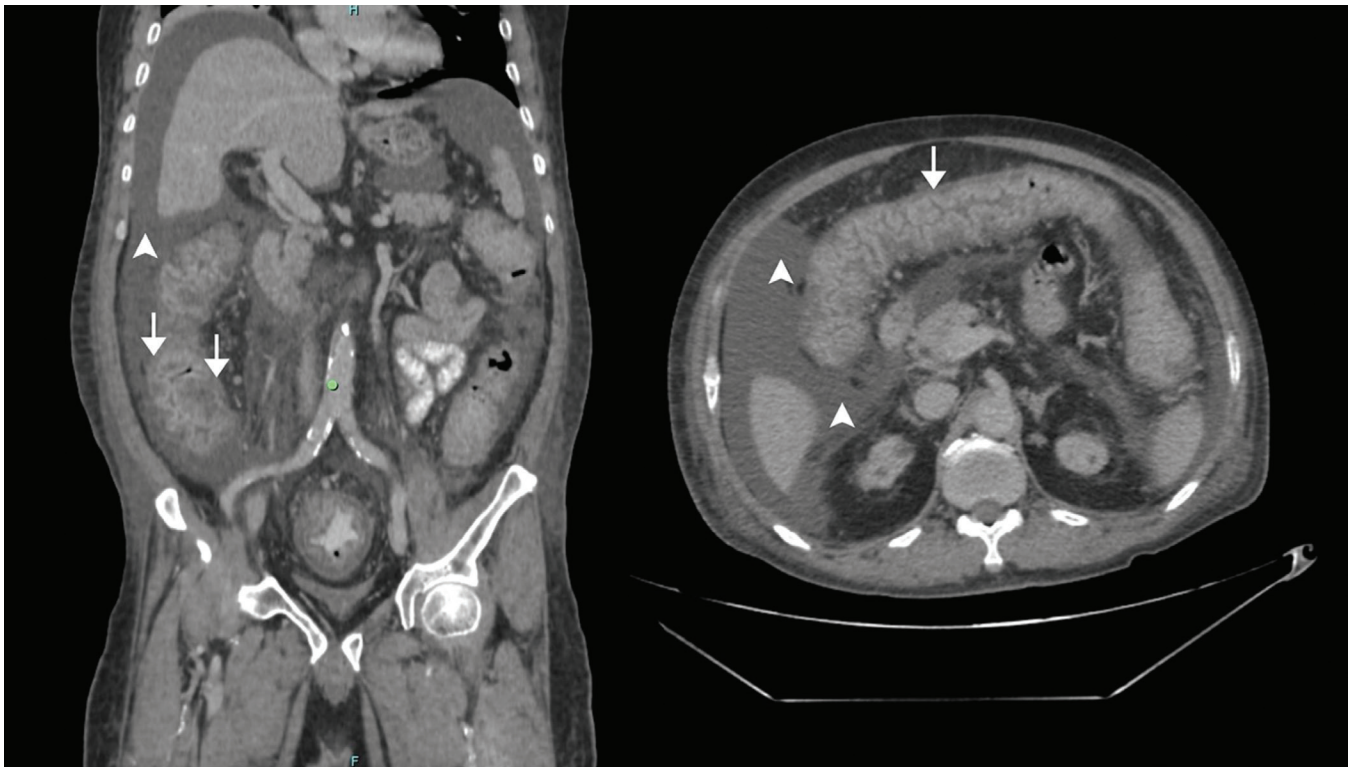

Figure 2. Abdominal CT scan with intravenous, oral, and rectal contrast revealed diffuse thickening and wall edema of the entire colon *(arrows)* with peritoneal free fluid *(arrowheads)*, consistent with *C. difficile* infection.

CDI during the COVID-19 pandemic has been mixed, with most retrospective studies indicating lower rates (1.4 to 4.4 cases per 10,000 patient-days) compared to that in the pre-pandemic period (3.3 to 9.3 cases per 10,000 patient days).[6] Incidence rates of CDI have been positively influenced by higher daily doses of antibiotics during the COVID-19 pandemic and negatively affected by more stringent infection prevention and control measures for COVID-19.[6,7] Based on retrospective studies in Poland and Italy, risk factors for developing CDI among patients with COVID-19 include previous hospitalization, comorbidities such as CKD, and receipt of antibiotics during hospitalization.[8,9] These risk factors were all present in our patient.

Clinical guidelines differ on specific recommendations regarding empiric antibiotic use among patients with COVID-19. The Philippine COVID-19 Living Recommendations issued a strong recommendation against the routine use of antibiotics among patients with severe to critical COVID-19.[3] The World Health Organization and the European Respiratory Society did not mention the subject in their latest COVID-19 clinical guidelines.[10,11]

In the case presented, procalcitonin was used to guide the patient's antibiotic therapy when he had COVID-19. Indirect evidence from randomized controlled trials done before the pandemic showed less duration of therapy and fewer antibiotic-associated side effects among patients who received procalcitonin-guided antibiotic treatment for respiratory infections compared to controls.[12] Whether procalcitonin may guide antibiotic treatment among patients with COVID-19 is still unclear. The National Institute of Health and Care Excellence (NICE) COVID-19 Guideline found insufficient evidence to recommend using procalcitonin to guide decisions about antibiotics.[13] The Philippine COVID-19 Guideline gave a strong recommendation against the use of procalcitonin as a basis for initiating antibiotic therapy. Instead, it recommended using a procalcitonin cut-off value of ≤0.25 ng/mL as a guide for discontinuing antibiotic treatment. However, this recommendation is based on very low certainty of evidence from two retrospective studies which showed both low sensitivity (40 to 50%) and specificity (65 to 88%) when using a procalcitonin cutoff of 0.25 ng/mL for detecting culture-positive bacterial infections in COVID-19 patients.[3]

This current case further highlights caution with the use of procalcitonin among patients with CKD undergoing hemodialysis. In the absence of infection, elevated levels of proinflammatory cytokines associated with renal impairment are postulated to account for higher baseline procalcitonin levels (0.26-1.0 ng/mL) in patients with CKD compared to levels (0.03-0.18 ng/mL) seen in healthy controls.[14] Moreover, procalcitonin levels have been reported to decrease after each hemodialysis session. These are essential considerations when interpreting procalcitonin levels in patients with COVID-19 and CKD.

CONCLUSION

Fulminant CDI is a potentially underreported complication of broad-spectrum antibiotic use in the local setting, as the proportion of COVID-19 patients who developed CDI has been estimated to be as high as 1% (95% CI, 1-2) in Europe and North America.[6] This highlights the need for physicians to keep a high index of suspicion for CDI among COVID-19 patients presenting with diarrhea. Procalcitonin-guided antibiotic therapy may reduce the antibiotic duration and antibiotic-associated side effects in patients with respiratory infections; however, clinicians must be familiar with the possible pitfalls and practice caution when interpreting procalcitonin levels, especially among patients with COVID-19 and CKD.

Statement of Authorship

All authors contributed in the conceptualization of work, acquisition and analysis of data, drafting and revising, and approved the final version submitted.

Author Disclosure

All authors declared no conflicts of interest.

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