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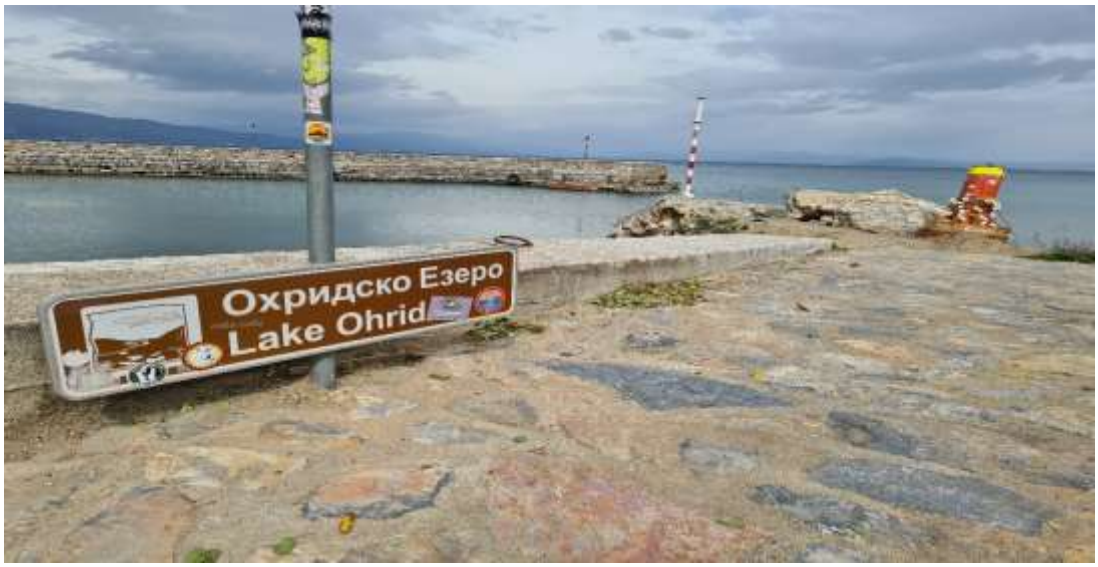

Proceedings of Supplement J. IMAB
Publications of papers presented in the Scientific Programme of the
14-th Southeast European Conference Infections and Cancer
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SECTION MEDICINE

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RECURRENT CLOSTRIDIOIDES DIFFICILE COLITIS – CASE REPORT

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ABSTRACT
Recurrent Clostridium difficile infection (rCDI) is usually defined as the reappearance of enteral symptoms 2-8 weeks after resolution of the initial episode with an appropriate therapy. Recurrence occurs in approximately 25% of patients within the first 30 days of the treatment. A 62-year-old female was initially hospitalized at our hospital within the intensive care unit (ICU) due to acute encephalitis and bilateral bronchopneumonia. Her comorbidities were diabetes mellitus and hypertension. She was treated with a combination of parenteral beta-lactam antibiotics for 35 days, acyclovir, probiotics, gastric suppression, and other supportive therapies. On the 18th hospital day, she developed diarrhea with liquid mucous green stools, prompting stool cultures and a C.difficile toxins test, which were negative and her condition stabilized spontaneously. A week later, she experienced a recurrence of enteral symptoms when stool cultures showed C.difficile positivity, but negative toxin tests. A colonoscopy was performed, revealing pseudomembranous pancolitis. Treatment continued with intravenous metronidazole and oral vancomycin for two weeks, alongside probiotics. This led to gradual improvement and normalization of stool consistency. Control cultures were C.difficile negative, and she was discharged after 49 days. Three weeks later, she complained of persistent watery stools and malaise, thus she was readmitted. New stool cultures confirmed C.difficile positivity with negative toxin tests. A repeat colonoscopy showed significant regression of pseudomembranous colitis and biopsy results indicated chronic nonspecific colitis. She was treated with probiotics, intravenous metronidazole for a week, and oral vancomycin. On first follow-up visit after three weeks, she returned asymptomatic with normal stools, and was advised to continue oral vancomycin, rifaximin, and probiotics. A second follow-up visit two weeks later confirmed normal stool characteristics. Prolonged use of antibiotics, extended hospital stays, advanced age, severe preexisting illness are significant risk factors for recurrent CDI. Prolonged oral vancomycin therapy has shown high efficacy in treatment of this serious condition.

Keywords: C.difficile, antibiotics, colitis, recurrence.

INTRODUCTION
Clostridioides difficile infection (CDI) is of great significance in hospitals worldwide and represents the most common cause of infectious diarrhea among hospitalized patients. It is a significant contributor to high morbidity and mortality, particularly among older adults. CDI is the leading cause of antibiotic-associated diarrhea [1]. Recurrent CDI (rCDI) is defined as the reappearance of symptoms 2–8 weeks after completing treatment, following symptom resolution with appropriate therapy. Approximately 25% of cases occur within the first 30 days aftertreatment cessation, less commonly, up to 2 months post-treatment. rCDI may be due to a relapse of the initial strain or reinfection with a new strain [2]. Risk factors include antibiotic use, advanced age, gastric acid suppression, hypervirulent strains, severe underlying illness and/or renal impairment, prior CDI history, severity of the previous CDI episode, prolonged hospital stay, and lack of adaptive immune responses to bacterial toxins A and B [3]. Diagnosis of CDI is based on history, physical examination, presence of risk factors, and fecal laboratory tests (EIA for *C. difficile* GDH antigen, EIA for toxins A and B, cell culture cytotoxicity assay, selective anaerobic culture, and nucleic acid amplification test). Adjunctive diagnostic tools include abdominal and pelvic imaging (contrast-enhanced CT) and lower gastrointestinal

endoscopy [4]. Treatment for rCDI depends on the recurrence. For the first recurrence in non-severe cases, oral metronidazole, vancomycin, or fidaxomicin are recommended, and for severe cases, oral vancomycin or fidaxomicin. Recommendations for second episode are a tapered/pulsed vancomycin or oral fidaxomicin and for the third or subsequent recurrences recommendations include fecal microbiota transplant (FMT) or oral fidaxomicin. Supportive care, such as correcting fluid and electrolyte imbalances, is crucial. Other therapeutic options include alternative antibiotics (rifaximin, nitazoxanide, teicoplanin), probiotics, intravenous immunoglobulin, monoclonal antibodies (actoxumab-bezlotoxumab), and anion-binding resins (tolevamer) [4]. However, despite modern diagnostic and therapeutic options, CDI remains a significant medical challenge.

We present a rare case of a patient with active C.difficile colitis on colonoscopy, despite multiple negative stool antigen and toxin tests, and then its reccurence.

CASE DESCRIPTION

A **62-year-old female patient** was initially hospitalized at our hospital within ICU department due to **acute encephalitis and bilateral bronchopneumonia** in a critical general condition. Her medical history included**insulin-dependent diabetes mellitus** and **arterial hypertension**.

First Hospitalization: The patient was admitted from September 23rd, 2022, to November 10th, 2022 (49 days). During this period, treatment included 35 days of parenteral beta-lactams(ceftriaxone 8 days than carbapenem 27 days), 21 days of acyclovir, pantoprazole, probiotic and other supportive therapy. Clinical Course:

- Day 18: The patient developed four episodes of liquid, green, mucous stools.
  - Laboratory results: Leu 11.5 × 10⁹/L, Neut 84%, Lymph 9%, Mono 7%, CRP 44 mg/L, sCreatinine 81 µmol/L.
  - Microbiology: Stool culture for Salmonella, Shigella, Campylobacter, Yersinia and for *C.difficile*as well as immunochromatographic test for toxins A/B were negative.
  - Symptomatic therapy led to spontaneous resolution within a few days.
- Day 32: Recurrence of four liquid, green, mucous stools.
  - Laboratory results**:** Leu 11.7 × 10⁹/L, Neut 92%, CRP 55 mg/L, sCreatinine 48 µmol/L.
  - Microbiology:Stool culture was negative; culture for *C. difficile* positive; test for toxin A/B was negative.
- Symptomatic therapy was initiated, but symptoms persisted, and the condition worsened.
- Day 35: Colonoscopy revealed pseudomembranous pancolitis (figure 1 and figure 2).

Beta-lactam antibiotics were discontinued, and the patient was started on intravenous metronidazole and oral vancomycin for 14 days. This resulted in gradual resolution of diarrhea, with normalization of stool frequency and consistency.

- Follow-up stool cultures were negative, and the patient was discharged.

Second Hospitalization:The patient was readmitted three weeks later, from December 2 to December 15, 2022 (11 days), with a 10-day history of watery, mucous diarrhea. The patient had been on nitrofurantoin for two weeks prior to admission for a urinary tract infection.

Initial Workup:

- Laboratory results: Leu 12.2 × 10⁹/L, Neut 64%, Lymph 19%, Mono 13%, CRP 42 mg/L, sCreatinine 29 μmol/L.
- Microbiology:Stool culture negative; *C. difficile* culture positive; toxin A/B test negative.

Clinical Course:

On December 9, 2022 (Day 7), colonoscopy showed significant regression of pseudomembranous lesions, limited to the cecum and rectum. Biopsy confirmed chronic non-specific inflammation. The patient was treated with:

- Intravenous metronidazole (500 mg three times daily for 7 days).
- Oral vancomycin in a tapered regimen: 125 mg four times daily for 10 days, 125 mg twice daily for 7 days, 125 mg once daily for 7 days, 125 mg every third day for 14 days.The initial portion of therapy was administered during hospitalization, with the remaining doses completed at home under guidance.

Follow-Up:

At the first follow-up, three weeks after the discharge, the patient reported no symptoms, with normal stool. Oral vancomycin tapering and rifaximin (200 mg three times daily for 14 days) were recommended, along with probiotics. At the second follow-up two weeks later, the patient remained asymptomatic, with normal stool characteristics.

DISCUSSION

CDI is one of the most commonly recognized healthcare-associated infections worldwide [1]. The disease spectrum ranges from non-severe to fulminant infection and death, where non-severe disease is characterized by watery diarrhea with three or more loose stools per day [4]. There are three different severity criteria for CDI based on SHEA/IDSA, ACG and hospital specific guidelines. They are: mild-moderate disease, severe disease and severe complicated [4]. Our patient met the criteria for mild-moderate disease. There is no single rapid test to diagnose CDI and diagnosis usually requires a multi-step diagnostic approach [5]. The current management for the diagnosis and treatment of CDI starts with clinical suspicion. Patients typically present with acute onset of diarrhea with more than 3 stools in a 24-hour period, fever, abdominal pain and leukocytosis, in the setting of recent antibiotic use and/or hospitalization [5]. Stool samples should be collected and sent for stool GDH antigen testing and for EIA toxin A and B testing. If testing is negative for either, then a nucleic acid amplification testing (NAAT) is done to confirm the diagnosis [4]. In our case, NAAT was not available. The EIA tests were negative all the time, however the clinical suspicion was still high and the decision was made for a diagnostic colonoscopy which ultimately revealed pseudomembranous colitis. Pseudomembranes are only found in 13% of patients who have CDI and are typically suggestive of severe infection [5]. Once she was started on appropriate antibiotics for CDI, her symptoms improved. The fact that our patient got better after the treatment further confirms that C.difficile was the culprit of her pseudomembranes. The exact mechanism for why patients can have multiple negative stool testing for CDI but still have endoscopic evidence of active C.difficile-mediated pseudomembranous colitis remains a conundrum and more research is needed for it to be elucidated.

CONCLUSIONS

The prolonged use of broad-spectrum antibiotics, prior and extended hospitalization, advanced age, severity of pre-existing conditions, and comorbidities are among the most significant risk factors for the development of recurrent *Clostridioides difficile* infection (rCDI) in hospitalized patients. A prolonged oral vancomycin regimen demonstrates high efficacy in the treatment of recurrent CDI. Although pseudomembranes in the colon are non-specific, they are most commonly associated with *C. difficile* colitis especially in the appropriate clinical setting where there is a high index of suspicion. In rare instances patients can have multiple false negative tests for *C. difficile* due to unclear reasons. Thus, it is necessary to consider the use of direct

visualization of the colon by endoscopy in such cases, to facilitate accurate diagnosis and to implement prompt and appropriate treatment.

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