Delayed Diagnosis of *Clostridium difficile* Colitis in a 48-Year-Old Woman with a Homozygous Mutation of the UGT1A1 Gene While on Chemotherapy for Colorectal Carcinoma

**Patient:** Female, 48-year-old

**Final Diagnosis:** *Clostridium difficile* colitis

**Symptoms:** Diarrhea

**Medication:** —

**Clinical Procedure:** Chemotherapy

**Specialty:** Oncology

**Objective:** Unknown etiology

**Background:** There are many causes of chronic colitis and diarrhea, including the effects of chemotherapy. Mutations in the UGT1A1 gene can be associated with increased toxicity from irinotecan-based chemotherapy. This report is of a case of delayed diagnosis of *Clostridium difficile* (*C. difficile*) colitis in a 48-year-old woman with a homozygous mutation of the UGT1A1 gene treated with chemotherapy for colorectal carcinoma.

**Case Report:** A 48-year-old woman with a low-differentiated colonic adenocarcinoma was treated after surgery with irinotecan, 5 fluorouracil, and panitumumab and had a history of chronic and severe diarrhea. Genetic testing identified a mutation in the UGT1A1 gene associated with increased toxicity to irinotecan, and the EIA tests performed for evaluation of *C. difficile* toxins A and B showed repeatedly negative results. Replacement of irinotecan with oxaliplatin did not have significant therapeutic results, but these were achieved by the administration of active antibiotics against *C. difficile* (metronidazole, vancomycin, and fidaxomicin).

**Conclusions:** This report has shown that in complex cases where patients are treated with chemotherapy and have increased susceptibility to drug toxicity, chronic diarrhea may still have an infectious cause. Only when the diagnosis is correctly made can the patient be appropriately treated.

**Keywords:** Antidiarrheals • Antineoplastic Combined Chemotherapy Protocols • Colorectal Carcinoma-Associated Antigen, Human

**Full-text PDF:** [https://www.amjcaserep.com/abstract/index/idArt/934361](https://www.amjcaserep.com/abstract/index/idArt/934361)
Background

We report the very complex case of an oncology patient who had damage caused by tumor cells adding to the immunosuppression generated by chemotherapy, in addition to the possible complications of the surgeries performed to remove the tumors and broad-spectrum antibiotic therapy used after surgery.

Although there are recommended treatments for intestinal toxicity induced by chemotherapy, like loperamide, codeine, STH, cholestyramine, Debridat, and strict diet [1], abandonment of a line of chemotherapy due to severe adverse effects is quite common [2]. The chemotherapeutic regimens most associated with diarrhea are 5fluorouracil and irinotecan [3].

There is a genetic sensitivity to the toxicity of these substances used in chemotherapy. So, although it seems that there is no significant difference in response rate after chemotherapy with FOLFOX among the wild-type, mutant type of UGT1A1*28, and UGT1A1*6, the UGT1A1*6 mutations had a higher risk of 3~4 grade diarrhea and neutropenia than those with wild-type [4].

Although chemotherapy-induced diarrhea has been reported as an adverse effect in up to 82% of patients with cancer [2], mainly associated with regimens targeting colorectal cancer (CRC) [1], gastrointestinal toxicity is not the only mechanism of this often-lethal complication of chemotherapy.

An underestimated cause of diarrhea in cancer patients undergoing chemotherapy is Clostridium difficile (C. difficile) infection (CDI). The clinical aspect of the diarrhea is similar for CDI and irinotecan severe toxicity [3] as well. The prevalence of C. difficile colonization is high in preoperative colorectal cancer patients, and the colonization is not necessarily acquired in the hospital [5]. C. difficile has become a serious medical and epidemiological problem, and is the most common cause of healthcare-associated diarrhea in developed countries [6].

Considered the most important pathogen in hospitalized patients, CDI is significantly more common in patients with malignancy due to several risk factors, including postoperative antibiotic therapy, hospitalization in a long-term health care facility, immunosuppression induced by chemotherapy, use of proton pump inhibitors, malnutrition, and non-specific inflammatory bowel diseases such as irritable bowel syndrome (IBS) [6].

The most commonly used method of diagnosing C. difficile infection is to identify A and B toxins by an enzyme immunoassay (EIA) test, which gives quick results. However, the sensitivity of EIA is low (75-85%) although the specificity is high (95-100%) [7]. Due to the poor performance of EIA tests, glutathione dehydrogenase (GDH) immunoassays have been developed [8]. The GDH test detects the metabolic enzymes present in all Clostridium difficile isolates, with high sensitivity but is not specific to C. difficile toxin-producing strains, and it is also present in non-toxin-producing C. difficile bacteria. Therefore, the recommendation for CDI diagnosis is a combination of these 2 tests (GDH and EIA) [4]. Higher sensitivity (80-100%) and specificity (87-99%) compared with the EIA test is obtained with the nucleic acid amplification test (NAAT), used starting in 2009 to detect the CDI gene.

The algorithm for diagnosing CDI assumes that a negative EIA for A and B toxins test when combined with a positive GDH test does not necessarily rule out C. difficile infection. In this case, it is indicated to perform a NAAT test or cultures of toxin-producing C. difficile, and only in the event of a negative response can the infection be refuted; otherwise, it is considered positive [6].

In the updated guidelines for CDI, it is recommended that, in the presence of clinical symptoms with at least 3 stools within 24 h, with a history of exposure to antibiotics, the best further evaluation is a multi-step algorithm, which has greater accuracy compared to single-step testing. In these guidelines, the definition for CDI includes symptoms and a positive stool test for C. difficile toxin, or detection of a toxin-producing C. difficile strain, or a typical endoscopic image, or pathology study confirming pseudomembranous colitis [6,8].

This report presents a case of delayed diagnosis of C. difficile colitis in 48-year-old woman with a homozygous mutation of the UGT1A1 gene, treated with chemotherapy for colorectal carcinoma.

Case Report

A 48-year-old-woman, diagnosed with irritable bowel syndrome (IBS) from a young age, but no other pathology, was operated due to a preliminary diagnoses of acute abdomen/ileus. An 8-cm obstructive mass was seen in the sigmoid colon during the intervention, so left hemicolectomy and left adenectomy were performed using a mechanical colo-recto-anastomosis circular stapler. Pathology showed low-differentiated colonic adenocarcinoma. PET/CT showed abnormally increased FDG uptake present in 3 lymph nodes in the paraaortic region, the left common iliac region, and the left supraclavicular region.

After investigations, the diagnosis was operated sigmoid colon adenocarcinoma, pt4N2M1, MSI-stable, KRAS/NRAS/BRAF wild-type, NTRK-negative. The PDL1 combined positive score (CPS): was 30% HER2-negative.

The therapeutic plan was to continue systemic treatment for 3 months (6 courses) with irinotecan (180 mg/m²), 5 fluorouracil and STH. After a 6-month period (24 h, with a history of exposure to antibiotics, the best further evaluation is a multi-step algorithm, which has greater accuracy compared to single-step testing. In these guidelines, the definition for CDI includes symptoms and a positive stool test for C. difficile toxin, or detection of a toxin-producing C. difficile strain, or a typical endoscopic image, or pathology study confirming pseudomembranous colitis [6,8].

This report presents a case of delayed diagnosis of C. difficile colitis in 48-year-old woman with a homozygous mutation of the UGT1A1 gene, treated with chemotherapy for colorectal carcinoma.
Delayed diagnosis of Clostridium difficile colitis

Caramoci A. et al.
Delayed diagnosis of Clostridium difficile colitis
© Am J Case Rep, 2022; 23: e934361

(2800 mg/m²), and panitumumab (6 mg/kg body weight). After that period, it was indicated at PET-CT follow-up.

One day before the first chemotherapy session, the patient presented a few episodes of diarrhea, which worsened every day until there were 8-10 watery stools/day, especially at night, with pains, cramps, and nausea. Her diarrhea persisted during the first 3 months of chemotherapy despite specific treatments for chemotherapy toxicity like loperamide, codeine, STH, cholestyramine, Debridat, and strict diet. The patient lost 10-12 kg weight. C. difficile infection was investigated by testing for toxins A and B (the enzyme immunoassay test – EIA) in stool and was negative during this period. The fecal culture was also negative for other pathogens or parasites.

The chemotherapy was postponed until resolution of severe colitis and cure of the etiology, which was suspected to be ischemic, infectious, or toxic due to chemotherapy. In the comparison of the previous images, the PET/CT investigation showed increased dimensions of the left supraclavicular lymph node, while its activity uptake was reduced and the paraaortic and left common iliac lymph nodes had slightly reduced activity uptake, but dimensions were similar to the previous findings.

A colonoscopy was performed to clarify the etiology of diarrhea and showed severe ulcerated colitis, in which the rectum was relatively normal up to 20 cm, and proximal parts were involved.

Genetic tests associated with toxicity at 5-Fluorouracil and irinotecan were performed and indicated negative DYPD A and MTHFR T allele, while the UGT1A1 polymorphism test showed the patient was a carrier of 2 alleles with 6 TA repeats (homozygous 6,6) in the UGT1A1 gene promoter, causing a genetic influence on sensitivity to irinotecan.

The investigations for C. difficile were repeated: another EIA test for toxins A and B was negative, but the GDH test was positive. The leucocytes were high (WBC 13 250/mcL).

The findings showed that the patient’s severe colitis situation suggested irinotecan toxicity.

The patient had received antibiotic therapy with metronidazole (1 g/day) and ciprofloxacin (1 g/day) for infection secondary to colitis. After 4-5 days of antibiotic treatment, the diarrhea was improved significantly and, after 10 days of antibiotic therapy and 4 weeks after chemotherapy, her diarrhea and abdominal pain completely resolved. Her appetite improved and a control colonoscopy showed a significantly decreased inflammation compared with 2 weeks before. Also, during the second colonoscopy, the fecal microscopy resulted in normal findings, as did biochemistry.

The chemotherapy was started again but, because it was supposed that the colitis was due to chemotherapy drugs, especially to irinotecan, this drug was replaced with oxaliplatin, and 5-Fluorouracil was stopped. Five days after the first session of oxaliplatin (130 mg/m²) and panitumumab (9 mg/kg body weight), the diarrhea returned. Another gastroenterologist was consulted, and his opinion was that this episode was a C. difficile relapse, so he prescribed vancomycin (oral, 250 mg/6 h) and metronidazole (oral, 500 mg/12 h) for 14 days. The treatment with vancomycin and metronidazole had excellent results, but after 1 month, under the chemotherapy regimen, the diarrhea reappeared. This time, vancomycin and metronidazole did not have satisfactory results. The patient took fidaxomicin (200 mg/12 h) for 10 days and continue fidaxomicin as pulse therapy (200 mg/2 days), with very good results.

Unfortunately, although the patient had no diarrhea associated with fidaxomicin with oxaliplatin and panitumumab and her general condition was much better, the PET-CT follow-up after another 3 months showed progression of dimensional and metabolical left supraclavicular lymph node, paraaortic area, and the left common iliac region.

This time, due to the repeated response to antibiotics, the diarrhea was considered probably CDI-related, thus allowing the possibility to again try irinotecan, which had previously stabilized the disease. The recommended protocol was irinotecan, 5-Fluorouracil, and bevacizumab with irinotecan started at a lower dose (80%). Antibiotics were continued in parallel (fidaxomicin as pulse therapy). Stereotactic body radiation therapy (SBRT) was performed for the foci of the left supraclavicular lymph node, paraaortic area, and the left common iliac region.

Two months after SBRT and 4 courses of irinotecan (142 mg/m²), 5-Fluorouracil (2800 mg/m²) and bevacizumab (5 mg/kg body weight), a clinical examination revealed good general condition, no problems, weight gain of 13 kg, ECOG (Eastern Cooperative Oncology Group) performance status 0, biochemistry with regression of tumor factors (Ca 19.9: 18 U/ml) and normal values of other biochemistry tests, and PET/CT with no pathologic activity in left supraclavicular, abdominal paraaortic, and left common iliac regions. We concluded that the patient had a complete response.

Discussion

This case emphasizes the importance of the differential diagnosis of toxic colitis induced by chemotherapy with other common etiologies of severe or refractory diarrhea in patients with malignancy.

When the history of the oncological patient includes surgical interventions followed by broad-spectrum antibiotic therapy,
the possibility of a _Clostridium difficile_ infection must be considered and evaluated very carefully. All the risk factors for CDI were present in this case report, yet the diagnosis was difficult for some important reasons.

First of all, a careful analysis of the anamnesis could have drawn attention to the onset of diarrhea that preceded, by 1 day, the first chemotherapy session.

On the other hand, though the genetic test for toxicity at 5Fluorouracil and irinotecan showed that _DPYD_ A allele and _MTHFR_ T allele were negative [9], the _UGT1A1_ polymorphism test showed that the patient was a carrier of 2 alleles with 6 TA repeats (homozygous 6,6) in the _UGT1A1_ gene promoter, causing sensitivity to irinotecan [10,11]. However, it was unlikely to have caused this severe form of diarrhea alone. Furthermore, the medication usually used for intestinal toxicity induced by chemotherapy [1] did not give any result, not even a minor or temporary improvement.

Another possible clinical clue of the non-toxic etiology of colitis could have been the recurrence of severe diarrhea when the chemotherapeutic drugs were changed entirely (Irinotecan and 5 Fluorouracil). Even though other chemotherapeutic regimens have been associated with diarrhea, they have been at a considerably lower rate than either 5Fluorouracil or Irinotecan [3].

The most critical reason for delaying the diagnosis of CID was the ambiguous results of paraclinical tests.

In this case report, EIA tests' failure to detect A and B toxins was interpreted as CDI-negative, despite the positive GDH test result and NAAD test not being performed. The EIA test, the most commonly used method, with quick results, has poor performance and must be used only in conjunction with other tests like GDH and NAAT as part of a multi-step diagnostic algorithm. This algorithm assumes that a negative EIA for A and B toxins test when combined with a positive GDH test does not necessarily rule out _C. difficile_ infection. The best way of evaluating a CDI is a multi-step algorithm, with greater accuracy compared to single-step testing. So, if CDI is suspected, it is indicated to perform a test NAAT or cultures of toxin-producing _C. difficile, not just an EIA for A and B toxins.

Furthermore, the first colonoscopy report failed to admit the macroscopic images of ulcerative colitis like a pseudomembranous aspect associated with CDI. Unfortunately, the microscopic pathology study was performed only after the second colonoscopy, 10 days after metronidazole treatment administered as an adjuvant to toxic colitis and not as an etiological treatment for CDI.

Although clinical guidelines accept the increase in leukocyte counts above 15 000/mcL as a criterion for severity [12], it is likely that in the context of patients with immunosuppression caused by chemotherapy, this should be adjusted to lower values. In this case, the leucocytes were high (WBC 13 250/mcL) but did not meet the quantitative criterion of severity.

An important indication for the diagnosis of CDI was, in this complicated case, the prompt and repeated therapeutic response to active antibiotic drug. Even when resistance to one drug was found, the next drug took effect. In particular, the therapeutic response to fidaxomicin, which is a narrow-spectrum antibiotic for _C. difficile, allowed a therapeutic diagnosis even if the paraclinical one was doubtful (only GDH test positive).

We must also note that, in the context of chemotherapy, relapses of CDI and resistance to antibiotics quickly and repeatedly occurred. Therefore, it is probably appropriate to establish a particular antibiotic protocol for oncological patients with CDI because the immunosuppression produced by chemotherapeutic drugs creates a context that favors the rapid development of relapses and antibiotic resistance. It is difficult to propose a therapeutic strategy for treating patients with a similar course, but we suggest fidaxomicin as the first-line antibiotic and not vancomycin or metronidazole. Furthermore, pulse therapy may be more effective than continuous therapy because provides longer coverage to patients undergoing chemotherapy. In this case, a pulse therapy with fidaxomicin (200 mg/48 h) throughout the chemotherapy period was a success but with a high financial cost. Pulse therapy with vancomycin may be a better choice. New studies are necessary to evaluate this perspective.

Fortunately, in this case, establishing the correct etiology of severe colitis, although late, allowed a return to effective chemotherapy and complete response to treatment.

**Conclusions**

This report has shown that in complex cases where patients are treated with chemotherapy and have increased susceptibility to drug toxicity, chronic diarrhea may still have an infectious cause. Only when the diagnosis is correctly made can the patient be appropriately treated.
References:

1. Benson AB 3rd, Ajani JA, Catalano RB, et al. Recommended guidelines for the treatment of cancer treatment-induced diarrhea. J Clin Oncol. 2004;22(14):2918-26

2. Maroun JA, Anthony LB, Blais N, et al. Prevention and management of chemotherapy-induced diarrhea in patients with colorectal cancer: A consensus statement by the Canadian Working Group on Chemotherapy-Induced Diarrhea. Curr Oncol. 2007;14(1):13-20

3. Koselke E, Kraft S. Chemotherapy-induced diarrhea: Options for treatment and prevention. Journal of Hematology Oncology Pharmacy. 2012;2(4):143-51

4. Planche T, Aghaizu A, Hollman R, et al. Diagnosis of Clostridium difficile infection by toxin detection kits: A systematic review. Lancet Infect Dis. 2008;8:777-84

5. Zheng Y, Luo Y, Lv Y, et al. Clostridium difficile colonization in preoperative colorectal cancer patients. Oncotarget. 2017;8:11877-86

6. Kukla M, Adrych K, Dobrowolsk A, et al. Guidelines for Clostridium difficile infection in adults. Prz Gastroenterol. 2020;15(1):1-21

7. Jones BL, Wiuff C, Coia JE. UK laboratory diagnosis of Clostridium difficile infection: In a state of transition, confusion, or both? J Hosp Infect. 2012;81:216

8. Eastwood K, Else P, Charlett A, Wilcox M. Comparison of nine commercially available Clostridium difficile toxin detection assays, a real-time PCR assay for C. difficile tcdB, and a glutamate dehydrogenase detection assay to cytotoxin testing and cytotoxigenic culture methods. J Clin Microbiol. 2009;47:3211-17

9. Amirfallah A, Kocal GC, Unal OU, et al. DPYD, TYMS and MTHFR genes polymorphism frequencies in a series of Turkish colorectal cancer patients. J Pers Med. 2018;8(4):45

10. Wang Y, Shen L, Xu N, et al. UGT1A1 predicts outcome in colorectal cancer treated with Irinotecan and fluorouracil. World J Gastroenterol. 2012;18(45):6635-44

11. Lin Z, Li G, Xu J, Guo C, Huang H. Correlation between UGT1A1 gene polymorphism and irinotecan chemotherapy in metastatic colorectal cancer: A study from Guangxi Zhuang. BMC Gastroenterol. 2020;20(1):96

12. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for Clostridium difficile infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). Clin Infect Dis. 2018;66:e1-48