Severe fluoropyrimidine toxicity in a patient with rectal adenocarcinoma with *DPYD* c.2846A>T heterozygous mutation: A case report

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Abstract. Dihydropyrimidine dehydrogenase (DPD) is the key enzyme involved in fluoropyrimidine metabolism. Variants in the *DPYD* gene can lead to DPD deficiency, markedly increasing the risk of toxicity. The present report describes a case of a patient with rectal cancer treated with the CAPOX regimen (capecitabine and oxaliplatin) who developed grade 3 mucositis, fever, diarrhea and multi-organ dysfunction, necessitating prolonged intensive care unit support. The patient was managed with aggressive intravenous fluid therapy, a broad spectrum of antibiotics, antivirals and antifungal agents, extended use of granulocyte colony-stimulating factor and intensive anti-diarrheal treatment. Full clinical recovery was achieved, and the patient was discharged. Genetic analysis revealed a heterozygous c.2845A>T *DPYD* variant, known to be associated with fluoropyrimidine-related toxicity. The present case underscores the importance of early recognition of potential DPD deficiency and the essential role of prompt, intensive supportive care in managing severe fluoropyrimidine-related toxicities.

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer, with diagnoses made using clinical examination, colonoscopy with biopsy, pelvic magnetic resonance imaging (MRI) for local staging and computed tomography (CT) to detect distant metastases (1,2). According to GLOBOCAN 2022, rectal cancer accounted for 729,833 new cases globally, with an age-standardized incidence rate (ASR) of 7.1/100,000, and caused 343,817 deaths, corresponding to an ASR of 3.1/100,000 (3,4). CRC) represents 9-10% of all cancer diagnoses and ~9% of cancer-related deaths worldwide (3). Established risk factors for CRC include dietary and lifestyle exposures such as high intake of processed and red meat, obesity and excess body fat, alcohol consumption, tobacco use, low fiber intake, diets rich in processed foods and sugar-sweetened beverages, and physical inactivity (5-7). Non-modifiable factors include advanced age, family history of CRC, hereditary syndromes such as Lynch syndrome (hereditary nonpolyposis colorectal cancer) and familial adenomatous polyposis (FAP), as well as inflammatory bowel diseases, notably ulcerative colitis and Crohn's disease (8). Prognosis depends on tumor stage, lymph node involvement, metastatic spread, histological grade and response to neoadjuvant therapy, with early-stage disease generally associated with improved outcomes (9,10). Treatment is stage-specific: Early tumors may be managed with surgery alone, whereas locally advanced cases often require neoadjuvant chemoradiotherapy followed by surgery (11,12). Fluoropyrimidines, such as 5-fluorouracil and capecitabine, are commonly used in chemoradiotherapy regimens; they exert their antitumor effects primarily by inhibiting thymidylate synthase, thereby disrupting DNA synthesis, and by incorporating into RNA and DNA, leading to cytotoxicity in rapidly dividing tumor cells (13-15).

Fluoropyrimidines are commonly used chemotherapeutic agents for treating several types of solid tumor such as gastrointestinal, head and neck, and breast cancers (16). These agents are primarily metabolized by dihydropyrimidine dehydrogenase (DPD) (17). Fluoropyrimidine-based regimens with oxaliplatin or irinotecan are the standard treatment for colorectal cancer. DPD is the key enzyme in fluoropyrimidine metabolism, with *DPYD* gene variants causing DPD deficiency and increasing toxicity risk (18). Complete DPD deficiency is rare, occurring in 0.1-0.5% of the general population (19,20). Partial DPD deficiency is more common; heterozygous variant carrier rates have been reported in 3-8% of cases. Certain polymorphisms, particularly in the DPYD gene, are associated with partial loss of enzyme activity (21,22). Treatment-related mortality in patients with unrecognized DPD deficiency who receive fluoropyrimidines has been reported to be around 0.2-0.5% (19,23). The risk of fatal toxicity is increased 5-10-fold, particularly in carriers of severe DPYD variants (24). The presence of *DPYD* variants was reported to be significantly associated with increased treatment-related mortality [odds ratio, 34.86; 95% confidence interval (CI), 13.96-87.05; P<0.05] (25).

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The present study aimed to present a case of rectal cancer treated with the CAPOX regimen (capecitabine and oxaliplatin) and developing severe fluoropyrimidine toxicity due to the DPYD mutation.

Case report

A mass was detected in the mid-rectum during a colonoscopy performed on a 35-year-old male patient at Harran University Medical Faculty Hospital (Sanliurfa, Turkey, in November 2023 due to rectal bleeding (Fig. S1). The patient was admitted for advanced examination and treatment with a preliminary diagnosis of rectal cancer. The biopsy sample was fixed in 10% neutral formalin solution at room temperature for 18-24 h, embedded in paraffin and sectioned at a thickness of 2.5 μm. The sections were stained with hematoxylin and eosin using a Leica Autostainer XL. The preparations were examined under a light microscope (Olympus BX43). Glandular structures exhibiting cellular and structural atypia were observed, and the findings were consistent with adenocarcinoma. Abdominal and pelvic MRI and thoracic CT revealed locally advanced rectal cancer (Fig. S2). Therefore, the patient was started on neoadjuvant CAPOX chemotherapy (Oxaliplatin 130 mg/m^2 IV on day 1 + capecitabine 1,000 mg/m^2 orally twice daily on days 1-14, repeated every 21 days). By the 14th day of capecitabine treatment, the patient presented with a fever (38.5˚C), grade 3 oral mucositis, abdominal pain and grade 3 diarrhea. Laboratory findings revealed grade 3 neutropenia, grade 3 thrombocytopenia (according to Common Terminology Criteria for Adverse Events v6.0) (26), elevated international normalized ratio (INR) and grade 1 hyperbilirubinemia. Admission laboratory results are presented in Table I. DPD enzyme deficiency was suspected. Serological tests for hepatitis A, B, C, toxoplasmosis, rubella, cytomegalovirus, herpes virus and other agents, and brucella were negative. Stool examination showed no parasitic infections, and cultures were negative for rotavirus, adenovirus, *Giardia*, *Cryptosporidium*, *Shigella*, *Salmonella*, *E. coli*, *V. cholerae*, *Y. enterocolitica*, *E. histolytica* and *C. difficile* toxins A/B. Blood, urine and stool cultures were sterile.

At admission, treatment included granulocyte colony-stimulating factor (G-CSF), piperacillin-tazobactam, metronidazole, oral loperamide, glutamine and intravenous (IV) 0.9% NaCl. On day 5 of hospitalization, severe diarrhea (>20 episodes/day) led to acute kidney injury (creatinine, 1.44 mg/dl), electrolyte imbalances and hemodynamic instability, requiring ICU transfer. Oral nystatin was started for suspected candidiasis. Despite treatment, deep neutropenia and diarrhea persisted, requiring continuous IV fluids, loperamide and octreotide infusion. Furthermore, the cytopenia was closely followed. Grade 4 neutropenia (0.38x10^3/μl) presented on hospital day 2, with a nadir of 0.002x10^3/μl by day 8. With daily filgrastim, neutrophil counts normalized by day 17. Grade 4 thrombocytopenia (31x10^3/μl) developed by day 3, reaching 5x10^3/μl on day 9 despite platelet transfusions. Platelet counts recovered by day 24. Anemia (hemoglobin, 10.5 g/dl) was detected on day 8 and a transfusion was required. The recovery sequence was as follows: Neutropenia, thrombocytopenia and finally, anemia. Moreover, by day 4, an ongoing fever (38.4˚C) and elevated C-reactive protein (CRP) (36.8 mg/dl) prompted escalation to meropenem, linezolid and oral vancomycin administration for suspected typhlitis, along with fluconazole prophylaxis. Persistent fever and CRP elevation led to caspofungin initiation on day 12. On day 14, herpetic lip lesions were treated with ganciclovir. The patient received 18 units of platelets, 8 units of fresh frozen plasma and 4 units of erythrocytes. Due to ongoing abdominal symptoms, imaging was performed which revealed toxic megacolon (Figs. 1 and 2). Oral food intake was stopped, and parenteral nutrition was initiated.

Genetic testing was performed using Sanger sequencing to determine DPD deficiency, which was detected as heterozygous c.2846A>T (p.Asp949Val) in Exon 22 (Fig. S3). The fever resolved by day 15, diarrhea gradually subsided after day 20, and toxic megacolon improved (Fig. S4). Neutropenia, thrombocytopenia, renal dysfunction, INR and bilirubin levels normalized during follow-up. By day 28, all antibiotic, antifungal and antiviral treatments were discontinued as infection markers normalized. The patient achieved full clinical recovery and was discharged. Laboratory follow-up results are presented in Table II.

In February 2024, a follow-up abdominal MRI revealed a partial radiological response (Fig. S5). Based on this finding, the multidisciplinary tumor board recommended a low anterior resection, which was performed at the Department of General Surgery, Koç University Hospital, Istanbul, Turkey, Histopathological examination of the surgical specimen confirmed a partial tumor response (data not shown). Adjuvant chemotherapy was not administered due to the development of severe DPD deficiency. The patient was followed up with abdominal MRI and thoracic CT scans at 3-month intervals. The latest imaging modalities revealed no evidence of disease recurrence as of June 2025 (Fig. S6).

Discussion

DPD deficiency is a life-threatening complication of fluoropyrimidine-based chemotherapy (27). In a meta-analysis of eight cohort studies (n=7,365), four *DPYD* variants [c.1905+1G>A, c.2846A>T, c.1679T>G and c.1129-5923C>G (HapB3)] were notably associated with severe fluoropyrimidine-associated toxicity, with relative risks of 2.9 (95% CI, 1.8-4.6), 3.0 (95% CI, 2.2-4.1), 4.4 (95% CI, 2.1-9.3) and 1.6 (95% CI, 1.3-2.0), respectively (19). In a DPD deficiency study, c.2846A>T (Asp949Val) was associated with increased toxicity in 1.4% (30/2,116) of patients, who presented with neutropenia, nausea, vomiting, diarrhea and infection (28). Another study reported that all 10 patients with the 2846A>T variant were heterozygous, and 6/10 experienced grade 3-4 toxicities within the first two cycles (29). In the present case, heterozygosity at c.2846A>T was identified, and the patient developed grade 4 neutropenia, nausea, vomiting and diarrhea during the initial cycles of treatment, similar to previously reported cases. These toxicities typically begin with nonspecific symptoms such as neutropenic fever, mucositis and diarrhea (30), and in the patient in the present case, these emerged by day 14 of therapy. Previous research indicates that symptom onset generally occurs between days 10-24, with gastrointestinal involvement being common (31). Clinically, oncologists should remain vigilant for possible DPD deficiency in patients who present with

Table I. Laboratory test results.

Test	Result	Normal range
Leukocyte, x$10^3/\mu$l	2.6	4.0-10.0
Neutrophil, x$10^3/\mu$l	1.0	1.6-6.9
Lymphocyte, x$10^3/\mu$l	1.6	1.0-2.9
Hemoglobin, g/dl	15.1	12.0-18.1
Thrombocyte, x10^3/ul	67.0	142.0-424.0
Glucose, mg/dl	113.0	74.0-106.0
Urea, mg/dl	38.5	19.0-50.0
Creatinine, mg/dl	1.0	0.7-1.3
ALT, U/l	17.0	10.0-49.0
AST, U/l	21.0	0.0-34.0
ALP, U/l	43.0	46.0-116.0
GGT, U/l	16.0	0.0-73.0
Total bilirubin, mg/dl	1.4	0.3-1.2
Direct bilirubin, mg/dl	0.5	0.0-0.3
Albumin, g/dl	4.0	3.2-4.8
Sodium, mmol/l	133.0	132.0-146.0
Potassium, mmol/l	3.7	3.5-5.5
Calcium, mg/dl	8.0	8.7-10.4
Creatinine kinase, U/l	38.0	32.0-294.0
Lactate dehydrogenase, U/l	209.0	120.0-246.0
Serum reactive protein, mg/dl	0.3	0.0-0.5
INR	2.2	0.8-1.2
Prothrombin time, sec	25.0	10.5-15.5
Activated prothrombin time, sec	124.0	22.0-36.0

ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, alkaline phosphatase; GGT, γ-glutamyl transferase; INR, International Normalization Ratio.

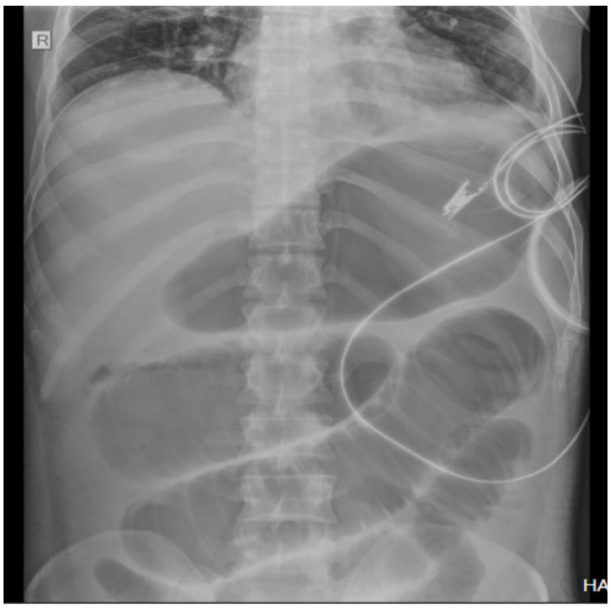

Figure 1. Appearance of toxic megacolon on direct abdominal radiography.

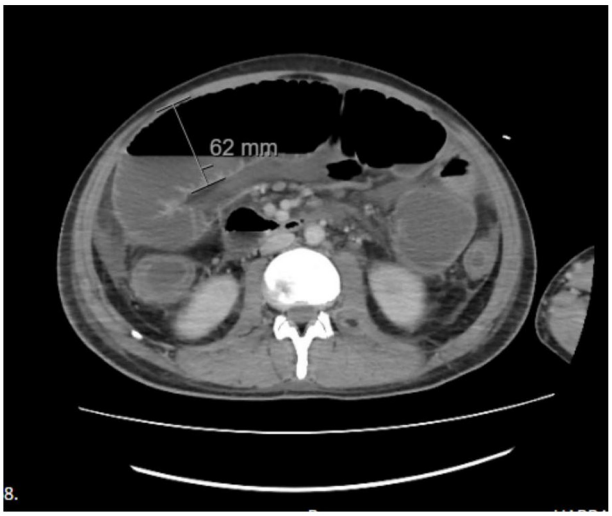

Figure 2. Appearance of toxic megacolon on CT imaging.

high-grade fluoropyrimidine-related toxicities, particularly in the early phase of treatment.

As the patient in the present case received CAPOX, we hypothesized that the clinical spectrum was attributable to oxaliplatin toxicity; however, the patient did not exhibit any neuropathy or cold paresthesias that could be associated with acute oxaliplatin toxicity. There was no acute hemolytic anemia associated with oxaliplatin due to predominance of direct bilirubin. Similarly, no elevations in alanine aminotransferase or aspartate aminotransferase were observed, suggesting acute liver toxicity associated with oxaliplatin. Indeed, genetic testing identified DPD deficiency, and the current clinical condition was attributed to this deficiency.

The present patient demonstrated worsening of symptoms despite aggressive treatment. The neutrophil count of the patient in the present case declined from 950 to 50/μl by day 3, reducing to 2/μl on day 8 despite G-CSF therapy. This profound neutropenia necessitated early broad-spectrum antibiotics. Therefore, piperacillin-tazobactam and metronidazole were initiated, later escalating to meropenem, linezolid and antifungal coverage. Despite extensive microbiological testing, no causative pathogen was identified. A previous report indicated fatal infection such as cytomegalovirus enterocolitis (32).

Severe diarrhea is another hallmark of severe fluoropyrimidine-associated toxicity. In the present case, the patient's diarrhea symptoms progressed from grade 3 to 4, requiring intensive care hospitalization. Despite loperamide and intravenous hydration, symptoms persisted, requiring high-dose octreotide infusion. This led to abdominal distension, ileus and toxic megacolon, and the diarrhea continued. Octreotide was suspected to contribute to these complications.

Furthermore, slight fluctuations in certain laboratory parameters (leukocyte, neutrophil, platelet, total and direct bilirubin) were observed; however, these were considered to be minimal with no notable clinical impact as the variations were within acceptable clinical and laboratory limits (Table II). The clinical condition of the patient remained stable despite these changes. Additionally, a search of the literature

Table II. Laboratory results of the patient during follow-up.

	Day																							
Test	1	2	3	4	5	6	7	8	9	10	11	13	14	15	16	17	18	20	21	23	24	26	29	30
Leukocyte, $10^3/\mu l$	2.6	1.3	0.8	0.7	0.6	0.4	0.5	0.6	0.5	0.6	0.7	1.7	2.3	3.3	4.5	7.2	9.9	11.5	12.9	12.2	10.2	6.2	5.1	4.9
Neutrophil, $10^3/\mu l$	0.9	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.3	0.6	0.7	1.6	2.5	3.5	4.5	6.7	8.0	7.6	3.2	2.2	1.7
Platelet, $10^3/\mu l$	67.0	58.0	31.0	12.0	25.0	38.0	25.0	15.0	5.0	27.0	20.0	22.0	19.0	50.0	31.0	25.0	49.0	59.0	50.0	98.0	144.0	192.0	285.0	381.0
Hgb, g/dl	15.0	15.0	16.0	15.5	15.0	13.2	12.1	10.5	9.4	8.1	10.0	9.5	9.9	7.9	10.6	11.2	11.2	11.2	11.3	10.9	10.2	9.1	10.4	10.5
Creatinine, mg/dl	1.0	0.8	1.0	1.1	1.4	2.0	2.6	2.2	1.7	1.4	1.0	0.9	0.7	0.7	0.6	0.7	0.5	0.6	0.6	0.6	0.6	0.6	0.5	0.6
ALT, U/l	17.0	17.0	15.0	13.0	17.0	19.0	18.0	22.0	23.0	15.0	21.0	19.0	23.0	41.0	42.0	43.0	43.0	52.0	54.0	48.0	43.0	28.0	25.0	21.0
Total bilirubin, mg/dl	1.4	1.7	3.1	4.6	6.2	5.5	6.2	5.8	5.6	5.7	6.1	5.4	5.2	3.8	4.2	4.4	4.1	3.7	4.3	3.2	2.2	1.8	1.3	0.9
Direct bilirubin, mg/dl	0.5	0.9	0.9	3.4	4.6	4.3	5.0	4.9	4.5	4.4	4.7	3.7	3.5	2.5	2.9	2.7	2.4	2.3	1.9	1.4	1.3	0.8	0.5	0.7
Albumin, g/dl	4.0	3.9	3.6	2.7	2.6	2.9	2.9	2.5	2.5	2.6	2.3	2.3	2.3	2.0	2.6	2.5	2.5	2.5	2.8	2.8	2.7	2.5	2.3	2.7
Sodium, mmol/l	133.0	136.0	131.0	120.0	119.0	122.0	124.0	137.0	148.0	155.0	152.0	148.0	147.0	140.0	135.0	133.0	134.0	132.0	132.0	131.0	133.0	134.0	138.0	137.0
Potassium, mmol/l	3.7	4.0	4.1	4.0	4.1	3.9	3.8	4.2	3.8	3.7	3.3	2.8	3.8	3.6	4.0	4.1	3.6	3.8	4.1	4.0	3.8	3.5	3.8	3.6
LDH, U/l	209.0	159.0	210.0	164.0	188.0	164.0	172.0	204.0	241.0	231.0	245.0	315.0	444.0	430.0	406.0	541.0	326.0	303.0	298.0	268.0	345.0	173.0	239.0	276.0
CRP, mg/dl	0.2	0.5	5.6	36.8	40.8	37.4	42.4	35.0	37.0	35.5	39.0	42.0	44.0	23.0	18.0	16.0	13.0	7.9	6.2	5.0	4.4	3.2	3.5	0.7
INR	2.1	1.0	-	-	1.8	1.9	1.8	-	2.2	1.8	1.9	-	1.7	1.3	1.2				1.2					
PT, sec	25.0	12.0	-	-	21.0	22.0	24.0	-	26.0	22.0	23.0	-	19.0	17.0	15.0				14.0					
APT, sec	124.0	19.0	-	-	26.0	38.0	28.0	-	27.0	28.0	27.0	-	28.0	26.0	25.0									

Hgb, hemoglobin; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CRP, serum reactive protein; INR, International Normalization Ratio; APT, activated prothrombin time.

revealed no research specifically addressing such fluctuations in laboratory values in patients with DPD deficiency.

Currently, routine *DPYD* genetic testing is not standard in several countries, including Turkey; however, the European Medicines Agency recommends pre-treatment screening to adjust dosing and prevent toxicity (24). In most regions, testing is performed retrospectively, potentially underestimating mortality (33). According to Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines, fluoropyrimidine dosing should be based on DPD activity assessed by uracil concentration and the dihydrouracil to uracil (UH2:Ura) ratio. Standard dosing is appropriate for normal DPD activity (uracil, <16 ng/ml;, UH2:Ura, >10). In partial DPD deficiency (uracil, ≥16 ng/ml and/or UH2:Ura, <10), a 50% dose reduction is recommended. In complete DPD deficiency, fluoropyrimidines should be avoided due to high toxicity risk (20).

Despite having a heterozygous DPYD mutation, the clinical course was severe, although severe diarrhea continued, toxic megacolon developed, and the patient was discharged with full recovery with long-term supportive treatment.

Moreover, there are certain limitations in the present case. Firstly, DPD activity measurement was not performed using the UH2:Ura ratio recommended for fluoropyrimidine dose modification according to the CPIC guidelines, and therefore adjuvant chemotherapy treatment was not administered. Secondly, a single case cannot clearly establish causality, estimate risk magnitude, or offer generalizable clinical recommendations based on case series.

In conclusion, patients with suspected DPD deficiency should be managed as immunosuppressed individuals, akin to stem cell transplant recipients. Intensive monitoring, broad-spectrum antimicrobial therapy, antifungals and aggressive supportive care, including blood transfusions and ICU admission, are crucial to improve outcomes in these high-risk patients.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

ST was the major contributor to writing the manuscript. ST and OK analysed the data and conceived and design of the study. ST and OK confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for the publication of the present case report.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, artificial intelligence tools were used to improve the readability and language of the manuscript or to generate images, and subsequently, the authors revised and edited the content produced by the artificial intelligence tools as necessary, taking full responsibility for the ultimate content of the present manuscript.

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