

[CASE REPORT]

Hematochezia Due to Panitumumab-induced Colitis with Vitamin K Deficiency

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Abstract:

Panitumumab, a fully human anti-epidermal growth factor receptor (EGFR) monoclonal antibody, has been shown to be useful in treating either advanced or recurrent *KRAS/NRAS/BRAF* wild-type colorectal cancer. We herein report the case of a 60-year-old man with short bowel syndrome who developed hematochezia due to panitumumab-induced colitis with vitamin K deficiency during third-line chemotherapy. The cause of vitamin K deficiency was the lack of intravenous vitamin K supplementation following a change from central venous nutrition to peripheral venous nutrition. We advise clinicians to carefully check for colitis and manage the infusions of chemotherapy patients with short bowel syndrome.

Key words: panitumumab, drug-induced colitis, hematochezia, vitamin K deficiency, short bowel syndrome

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Introduction

Panitumumab, a fully human anti-epidermal growth factor receptor (EGFR) monoclonal antibody, has been proven to be useful in the treatment of unresectable advanced or recurrent *KRAS/NRAS/BRAF* wild-type colorectal cancer, not only when used in combination with 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX), or with 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first- or second-line chemotherapy, but also as salvage monotherapy (1-3). Diarrhea has been reported to occur in approximately 20% of all patients receiving panitumumab monotherapy (4), and there have been no reports of hematochezia. Although the mechanism of diarrhea induced by anti-EGFR monoclonal antibody therapy remains unclear, one hypothesis points to excessive chloride secretion and deficient sodium absorption (5).

Vitamin K, a fat-soluble vitamin, is a necessary cofactor for the activation of coagulation factors II, VII, IX, X, and proteins C and S. Therefore, vitamin K deficiency leads to

bleeding tendency. The main causes of vitamin K deficiency are the lack of hepatic storage in newborns, liver insufficiency, malabsorption, dietetic deficiency, and the administration of antibiotics and coumarins (6).

Case Report

A 60-year-old man was transferred to our hospital with abdominal pain and hematochezia. He had a history of operable *KRAS/NRAS/BRAF* wild-type sigmoid colon cancer two years previously, for which he underwent resection of the primary lesion (Hartmann's operation) and colostomy of the descending colon. However, multiple peritoneal disseminations were observed intraoperatively. After the surgery, he received S-1 plus oxaliplatin (SOX) as first-line chemotherapy. Bevacizumab (BV) was then added to the second course of SOX therapy, but a small bowel perforation occurred 21 days after initiation. An artificial anus was made at the jejunum approximately 120 cm from the ligament of Treitz. Although oral intake continued, he developed short bowel syndrome and required central venous nutrition

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Figure 1. Computed tomography images during the previous hospital admission. A diffuse edematous wall of the colon is observed (A: ascending colon, T: transverse colon, D: descending colon, R: rectum).

(CVN) through a central venous access device (CVAD). SOX was re-administered without BV following the perforation. After 16 courses of SOX, he received FOLFIRI as a second-line chemotherapy; however, this was discontinued after one course because of drug-induced interstitial pneumonia.

The patient was started on panitumumab monotherapy as third-line chemotherapy, but developed a catheter-related bloodstream infection after the first course. The CVAD was removed, and peripheral venous nutrition (PVN) was initiated. He was also treated with antibiotics (tazobactam and piperacillin) for 11 days. Although the second course of panitumumab was administered during antibiotic administration, no diarrhea or abdominal pain occurred. The third course of panitumumab was started 22 days after the discontinuation of antibiotics. Three days after the re-administration of panitumumab, hematochezia was observed from the colostomy of the descending colon and anus. This was not observed in the artificial anus of the jejunum. After the fourth course of panitumumab treatment, the hematochezia worsened, and abdominal pain occurred. Computed

tomography showed a diffuse edematous wall of the colon (Fig. 1), and colonoscopy (CS) showed spontaneous bleeding of the entire colon, loss of vascular permeability, and rough mucosa (Fig. 2). He was transferred to our hospital 25 days after the onset of hematochezia. Laboratory studies at admission showed mild anemia, coagulation disorders, and a marked increase in protein induced by vitamin K absence or antagonist-II (PIVKA-II) levels. A stool culture test showed a normal bacterial flora and no growth of *Campylobacter jejuni*, enterohemorrhagic *Escherichia coli*, and *Klebsiella oxytoca* (Table 1, 2). There were no notable medications, including nonsteroidal anti-inflammatory drugs. Based on the clinical course and laboratory studies, bleeding due to vitamin K deficiency secondary to PVN was diagnosed. CVN containing 2,000 µg of vitamin K1 was administered immediately. The hematochezia resolved the following day. On the third day of hospitalization, his prothrombin time (PT) and activated partial thromboplastin time (APTT) improved, and his vitamin K1 and K2 levels returned to normal (Table 2). CS, performed on the 12th day of hospitalization, revealed a diffuse coarse mucosa with loss of vascu-

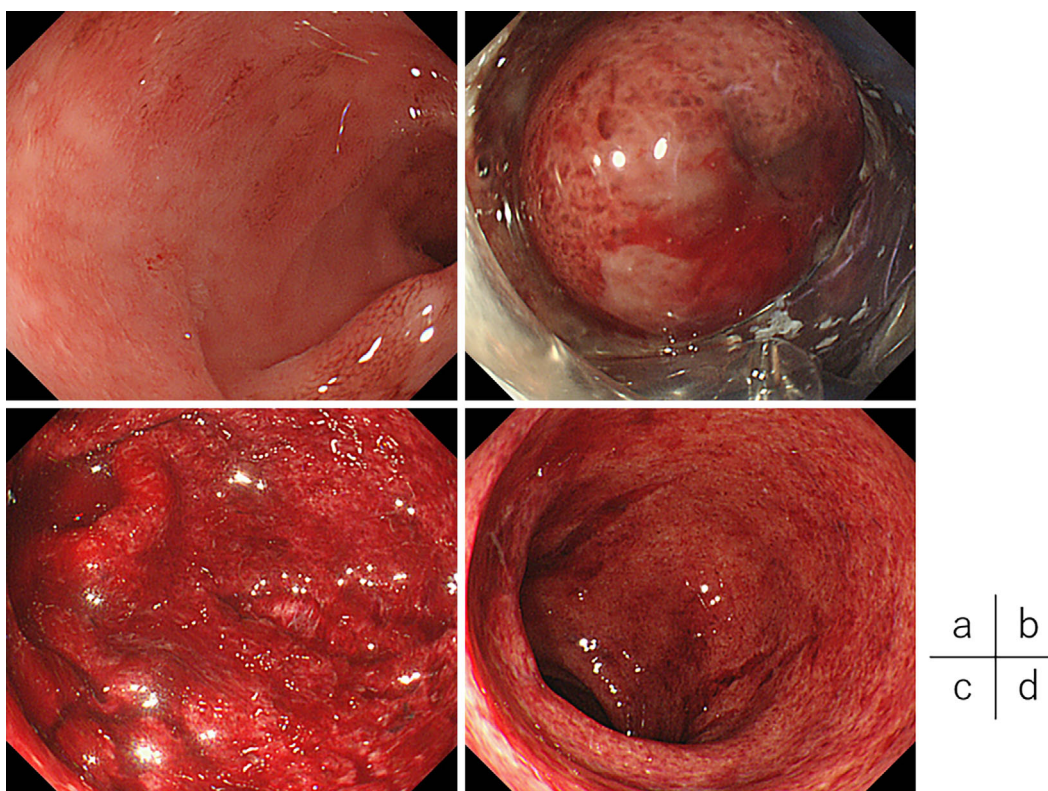


Figure 2. Colonoscopy findings during the previous hospital admission. (a: upper left) In the terminal ileum, a normal mucosa was seen. (b: upper right) At the artificial anus of the descending colon, mucosal redness and edema with ulcerations were seen. (c: lower left) In the ascending colon, spontaneous bleeding, loss of vascular permeability, and rough mucosa were seen. A mucosal laceration was seen by air infusion. (d: lower right) In the rectum, the findings were similar to those of the ascending colon.

Table 1. Laboratory Findings (Hematologic Test, Chemistry, and Laboratory Culture).

Hematologic test		Chemistry	
White blood cells	5,800 / μ L	AST	45 U/L
Neutrophil	74 %	ALT	46 U/L
Lymphocyte	20 %	LDH	317 U/L
Monocyte	5 %	ALP	895 U/L
Eosinophil	1 %	γ -GT	262 U/L
Basophil	0 %	Total bilirubin	1.1 mg/dL
Red blood cells	437 \times 10 ⁴ / μ L	Total protein	7.3 g/dL
Hemoglobin	12.4 g/dL	Albumin	3.8 g/dL
Platelet count	28.6 \times 10 ⁴ / μ L	BUN	16.2 mg/dL
		Creatinine	0.79 mg/dL
Laboratory culture		Sodium	146 mmol/L
Stool	normal flora	Potassium	3.4 mmol/L
		Chloride	105 mmol/L
		CRP	0.83 mg/dL
		Glucose	91 mg/dL

AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ -GT: γ -glutamyl transpeptidase, BUN: blood urea nitrogen, CRP: C-reactive protein

lar permeability and purulent mucus secretion; however, the bleeding showed improvement (Fig. 3). Biopsy specimens from the descending colon showed lymphocytic infiltration

of the mucosa, neutrophilic and eosinophilic tissue infiltration, and partial cryptitis. However, no apoptotic bodies were observed (Fig. 4). T lymphocytic infiltration of the epi-

Table 2. Laboratory Findings (coagulation).

Parameter	Normal value	Unit	Day 1	Day 3	Day 28
PT	10.5-12.5 s		20.0	13.0	12.1
PT-INR	0.85-1.15		2.23	1.19	1.10
APTT	25-35 s		48.0	31.3	27.3
Fibrinogen	200-400 mg/dL		323		
FDP	<5 µg/mL		5.2		
D-dimer	<1 µg/mL		1.51		
Coagulation factors activity					
II	75-135 %		55		
V	70-135 %		92		
VII	75-140 %		63		
VIII	60-150 %		154		
IX	70-130 %		86		
X	70-130 %		64		
Protein S activity	60-150 %		58		
Protein C activity	54-146 %		85		
PIVKA-II	<40 mAU/mL		17,227		68
Vitamin K1	0.25-1.25 ng/mL			2.33	
Vitamin K2	<0.10 ng/mL			Undetectable	

PT: prothrombin time, INR: international normalized ratio, APTT: activated partial thromboplastin time, FDP: fibrin/fibrinogen degradation products, PIVKA-II: protein induced by Vitamin K absence or antagonists-II

thelium or crypt was not observed on immunohistochemical staining. Although the endoscopic and histopathological findings were inconclusive, drug-induced lymphocyte stimulation test (DLST) for panitumumab was positive [stimulation index (SI) was 242%]. Based on the clinical course and results of the DLST and SI, a diagnosis of colitis induced by panitumumab and vitamin K deficiency was made. Panitumumab was discontinued, and vitamin K1 administration was maintained. No recurrence of hematochezia was observed thereafter, and the PIVKA-II levels returned to normal (Table 2). The patient was eventually transferred to the previous hospital on the 39th day.

Discussion

Drug-induced enterocolitis involves a variety of morphological and functional abnormalities in the small and large intestines following either short-term or long-term exposure to a drug. No clear diagnostic criteria currently exist, and the diagnosis is made based on a comprehensive evaluation of the patient's history, laboratory findings, and clinical course. The chemotherapy drugs most frequently associated with diarrhea are 5-fluorouracil (a thymidylate synthase inhibitor) and irinotecan (a topoisomerase I inhibitor) (7). Although 5-fluorouracil (5-FU) is one of the most widely used chemotherapy drugs, it causes intestinal mucositis with diarrhea, nausea, vomiting, and anorexia (8, 9). The mechanisms of intestinal mucositis due to 5-FU are believed to be a combination of several factors, including direct cytotoxicity, reactive oxygen, apoptosis, inflammatory cytokines, and

dysbiosis (10, 11). Irinotecan causes acute and late diarrhea. Acute diarrhea, which occurs within minutes to up to 24 hours after administration of irinotecan, is due to the inhibition of acetylcholine esterase. However, it can be easily controlled with atropine (7). One proposed mechanism for late diarrhea is that the active metabolite of irinotecan, SN-38, is 100 to 1,000 times more cytotoxic than the parent compound. In animals, irinotecan causes villous atrophy and crypt damage in the small intestine, severe colonic mucosal damage with crypt hypoplasia, and increased mucus secretion (12). Each chemotherapy drug presents with a different mechanism of diarrhea and colitis.

On the other hand, EGFR inhibitors, cetuximab and panitumumab, also cause diarrhea, but their mechanisms are unknown (7). Johann et al. suggested that the mechanism of diarrhea, caused by EGFR inhibitors, is secretory in nature and it inhibits EGFR effects on chloride secretion. However, more than one mechanism could be likely involved. As EGFR is expressed by epithelial cells throughout the gastrointestinal tract, possibilities include altered gut motility, colonic crypt damage, changes to intestinal microflora, altered nutrient metabolism, absorption, and altered transport in the colon (5).

In our case, bacterial colitis and antibiotic-associated hemorrhagic colitis (AAHC) were initially suspected. The former was ruled out on the basis of stool culture tests. The latter was also excluded because it differed from the characteristics of AAHC: *Klebsiella oxytoca* is cultured in a stool culture, onset is within a week from the start of antibiotic therapy, and the range of lesions is segmental without the

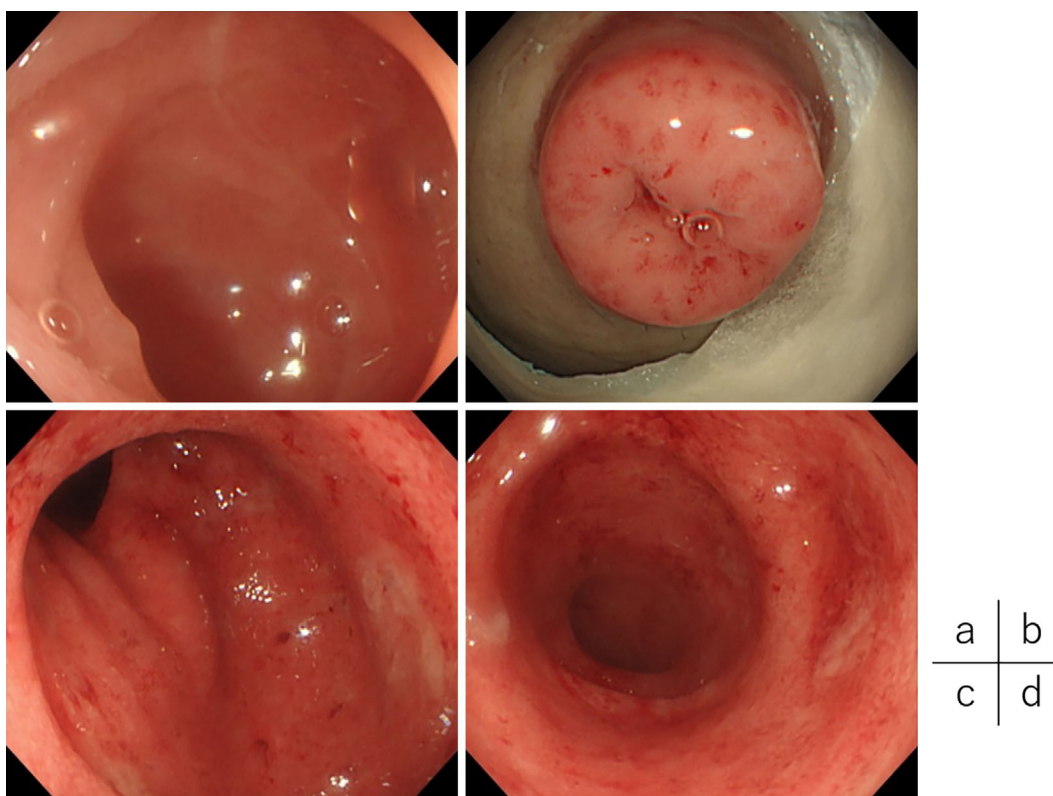


Figure 3. Colonoscopy findings 12 days after admission to our hospital. (a: upper left) In the terminal ileum, a normal mucosa was seen. (b: upper right) At artificial anus of the descending colon, a mild reduction in mucosal redness and edema were observed. (c: lower left) In the ascending colon, diffuse coarse mucosa with loss of vascular permeability and purulent mucus secretion were seen, but the bleeding improved. (d: lower right) In the rectum, the findings were similar to those of the ascending colon.

rectum (13). The side effects of 5-fluorouracil and irinotecan were completely ruled out because five months had elapsed since they were last administered.

Individual histological features such as apoptosis, eosinophilic tissue infiltration, and increased intraepithelial lymphocytes within the gut mucosa may suggest drug-induced enterocolitis, but these are not specific (14). Our findings of lymphocytic mucosal infiltration with neutrophilic and eosinophilic tissue infiltration were histopathologically inconclusive for the diagnosis of drug-induced colitis. However, panitumumab-induced colitis was strongly suspected based on the clinical course, given that the symptom onset was 3 days after the re-administration of panitumumab, hematochezia worsened with continuation of panitumumab, and the colitis improved with the subsequent discontinuation of panitumumab. This diagnosis was further supported by the positive DLST results for panitumumab.

The DLST is commonly used for suspected drug allergic reactions, but its accuracy differs depending on the target organ or drug. Saito et al. investigated the diagnostic accuracy of DLST for mesalazine allergy in 104 patients with ulcerative colitis by comparing the DLST results of 24 patients with a history of adverse events to mesalazine in 80 patients without. Symptoms of these mesalazine allergy include diarrhea, hematochezia, and abdominal pain (15). The SI of

each group was at $243.9\% \pm 291.1\%$ and $119.8\% \pm 53.0\%$, respectively, and the SI was significantly higher ($p=0.030$) in the group with known adverse events. DLST may also be useful for symptomatic cases. Based on the clinical course and DLST results (SI, 242%) in our case, we concluded that the patient had panitumumab-induced colitis. Saito et al. also reported that the period from the start of mesalazine administration to the onset was 14.3 ± 7.5 days (15). This is a shorter period than that in our case. These differences were based on whether the administration was daily or every two weeks. In our case, it may have been sensitized during the first or second course of panitumumab and elicited during the third course.

In our patient, coagulation abnormalities due to vitamin K deficiency manifested as hematochezia. Vitamin K is a fat-soluble vitamin that is chemically composed of 2-methyl-1,4-naphthoquinone. Vitamin K includes two natural vitamins, vitamin K1 and K2. Vitamin K1 is synthesized by plants and is mainly found in leafy green vegetables, while vitamin K2 is synthesized by intestinal bacteria and is found in animal-sourced foods. Vitamin K is absorbed in the jejunum and ileum. Being a cofactor of gamma-glutamyl carboxylase, it is required for the gamma-carboxylation of coagulation factors II (prothrombin), VII, IX, X, protein C, and protein S. Therefore, vitamin K deficiency or antago-

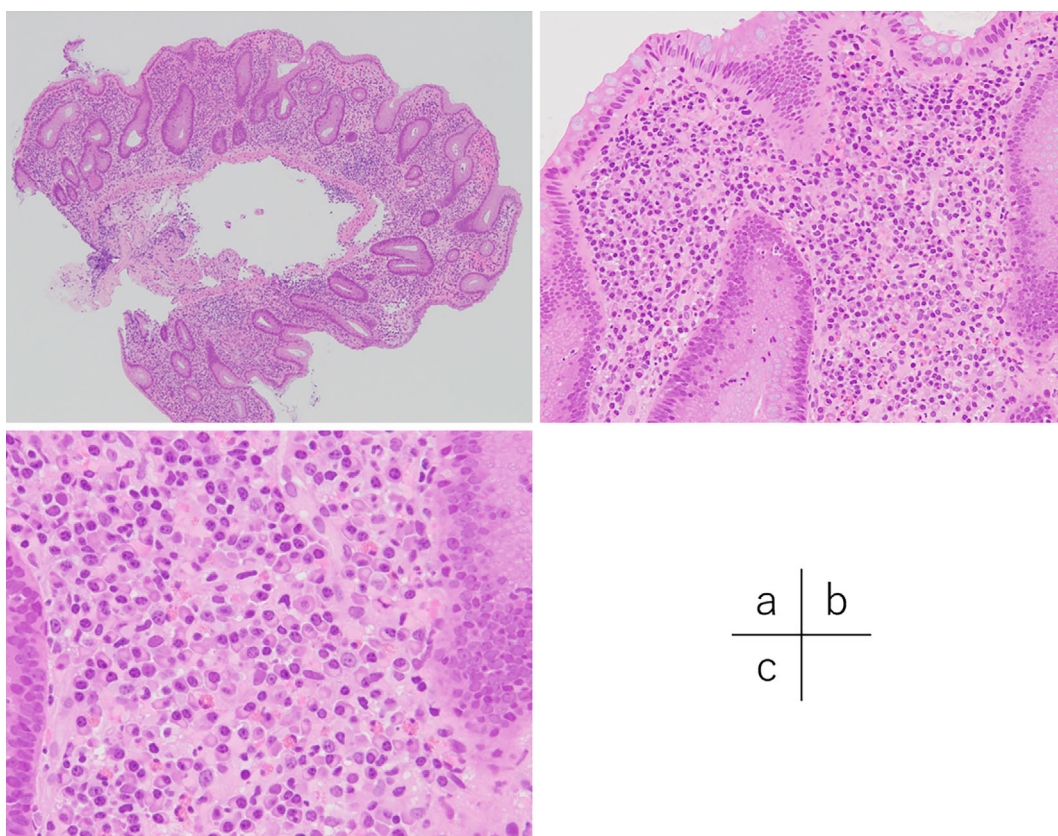


Figure 4. Histological findings of biopsy specimens from the descending colon (Hematoxylin and Eosin staining). (a: upper left) Active enteritis with erosive changes and partial cryptitis were seen ($\times 40$). (b: upper right) In the lamina propria, moderate to severe lymphoplasmacytic infiltration was observed ($\times 100$). (c: lower left) Intermingled neutrophils and eosinophils were also observed, but no definite apoptotic bodies were detected ($\times 400$).

nism causes a prolonged prothrombin time or bleeding and vitamin K administration promptly improves them (6, 16, 17). PIVKA-II is the product of insufficient carboxylation of prothrombin and is a highly sensitive marker of vitamin K deficiency (18).

In this case, the PT was prolonged, and PIVKA-II levels were markedly increased. In addition, hemochezia disappeared the day after intravenous vitamin K1 was administered. Furthermore, the levels of coagulation factors II, VII, IX, and X were reduced upon admission. Therefore, a diagnosis of vitamin K deficiency bleeding was made. Although oral intake was continued, the cause of vitamin K deficiency was the lack of intravenous vitamin K1 supplementation following the change from central to peripheral venous nutrition in the presence of short bowel syndrome. The administration of antibiotics may also interfere with vitamin K2 synthesis by intestinal bacteria.

To our knowledge, there are no reports of hemochezia secondary to panitumumab administration that have been published. The endoscopic images revealed spontaneous bleeding of the entire colon. Similar symptoms occur in panitumumab-induced colitis with vitamin K deficiency. In conclusion, clinicians are advised to carefully check for colitis and manage the infusions of chemotherapy in patients with short bowel syndrome.

The authors state that they have no Conflict of Interest (COI).

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