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【 CASE REPORT 】

Severe Colitis Caused by Hepatic Arterial Infusion Chemotherapy with Cisplatin for Hepatocellular Carcinoma

Shumpei Yamamoto, Hideki Onishi, Atsushi Oyama, Akinobu Takaki and Hiroyuki Okada

Abstract:
A 78-year-old man with chronic hepatitis C underwent hepatectomy for hepatocellular carcinoma (HCC) 11 years prior to presentation. He was diagnosed with multiple intrahepatic recurrences of HCC with portal vein invasion and received hepatic arterial infusion chemotherapy (HAIC) with cisplatin. He developed abdominal pain, diarrhea, and blood-stained stool following treatment. Computed tomography revealed significant bowel wall thickening throughout the colon. Colonoscopy revealed reddish edematous mucosa with a reduced vascular pattern without ischemic changes. Conservative treatment with total parenteral nutrition improved his condition and his imaging findings. This is the first report of severe colitis following HAIC with cisplatin.

Key words: colitis, hepatic arterial infusion chemotherapy, cisplatin

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Introduction

Chemotherapy-induced gastrointestinal toxicity is a common complication in patients with cancer (1-7). Neutropenic enterocolitis, ischemic colitis, and pseudomembranous colitis are the specific types of colitis that are known complications of chemotherapy (3-8). In Japan, a fine-powder formulation of cisplatin is commonly used to administer hepatic arterial infusion chemotherapy (HAIC) for transcatheter arterial chemoembolization (TACE)-refractory hepatocellular carcinoma (HCC) (9, 10). General chemotherapy with cisplatin may occasionally cause colitis (particularly neutropenic colitis) (6, 8); however, no report has described colitis secondary to HAIC with cisplatin because the dosage of cisplatin used for HAIC is relatively small.

We herein report the first case of a patient with severe colitis that occurred secondary to HAIC with cisplatin. In this case, the colitis could not be classified into any specific type of chemotherapy-induced colitis. Although we were unable to accurately determine the pathomechanism contributing to colitis, improvement in the colonoscopic findings of edematous reddish mucosa and the immediate symptomatic improvement in the patient implicated allergic colitis as a contributor. This case emphasizes that physicians should consider colitis as a complication in patients developing abdominal pain after HAIC with cisplatin.

Case Report

A 78-year-old man with chronic hepatitis C was diagnosed with HCC affecting segment 8 and underwent hepatectomy 11 years prior to presentation. Intrahepatic recurrence was identified three years after resection. He reported a history of diabetes and acute myocardial infarction, appendectomy, and prostate cancer. Furthermore, he had been taking clopidogrel and low-dose aspirin. He underwent several sessions of radiofrequency ablation and TACE over eight years after the recurrence; however, ultrasonography and contrast-enhanced computed tomography (CECT) revealed multiple intrahepatic recurrences with portal vein invasion of the P5 branch (Fig. 1). Therefore, he was hospitalized and underwent the first session of hepatic arterial infusion (HAIC) using a fine-powder formulation of cisplatin (IA-call®). Abdominal angiography revealed the thread and streaks sign at the P5 branch, which implied a vascularized

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tumor thrombus (Fig. 2a). CT hepatic arteriography in the early and delayed phases also showed HCC with a portal vein tumor thrombus of the P5 branch (Fig. 2b, c).

He was asymptomatic, and his vital signs were within the normal ranges. Laboratory investigations revealed an elevated serum alpha-fetoprotein level of 995 ng/mL and a des-γ-carboxy prothrombin level of 95 mAU/mL. His serum creatinine level was within the normal range; however, his serum albumin level and platelet count were reduced (Table 1). His liver function was categorized as Child-Pugh class B (7 points).

HAIC was administered with 70 mg cisplatin based on his body surface area via the anterior branch of the right hepatic artery for over 30 minutes without any complications.

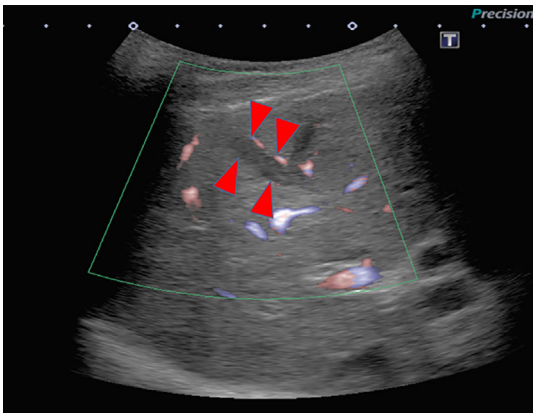

Figure 1. Color Doppler ultrasonographic image showing a solid tumor in the portal vein (red arrowhead).

Cisplatin was solubilized in saline at a concentration of 100 mg/70 mL without lipiodol. However, he developed abdominal pain the day following HAIC administration, with diarrhea on the third day and the passage of a small quantity of blood-stained stool on the sixth day. His white blood cell count and serum C-reactive protein levels gradually increased (Fig. 3). CECT performed on the sixth day showed significant bowel wall thickening between the cecum and the rectum with a disproportionate degree of fat stranding around the cecum and the sigmoid colon. An edematous gastric wall was also observed; however, the small bowel wall was normal (Fig. 4). No contrast failure was observed throughout the colon and the small bowel mucosa, and no arterial occlusion and venous thrombosis were detected. Colonoscopy performed on the seventh day showed reddish edematous mucosa with a reduced vascular pattern throughout the colon (Fig. 5). Although multiple erosions were observed, no ischemic changes were identified. The part of the terminal ileum that we could observe was normal. Laboratory investigations did not reveal neutropenia. Cytomegalovirus IgG/IgM and polymerase chain reaction tests showed negative results. Serum levels of beta-D glucan and procalcitonin were not elevated. Stool and blood cultures revealed negative results, and the *Clostridium difficile* toxin test also revealed negative results. Although the drug-induced lymphocyte stimulation test (DLST) for cisplatin showed a negative result, considering the patient's clinical course, we speculated that colitis might have occurred secondary to cisplatin administration.

He received total parenteral nutrition (TPN) for bowel rest

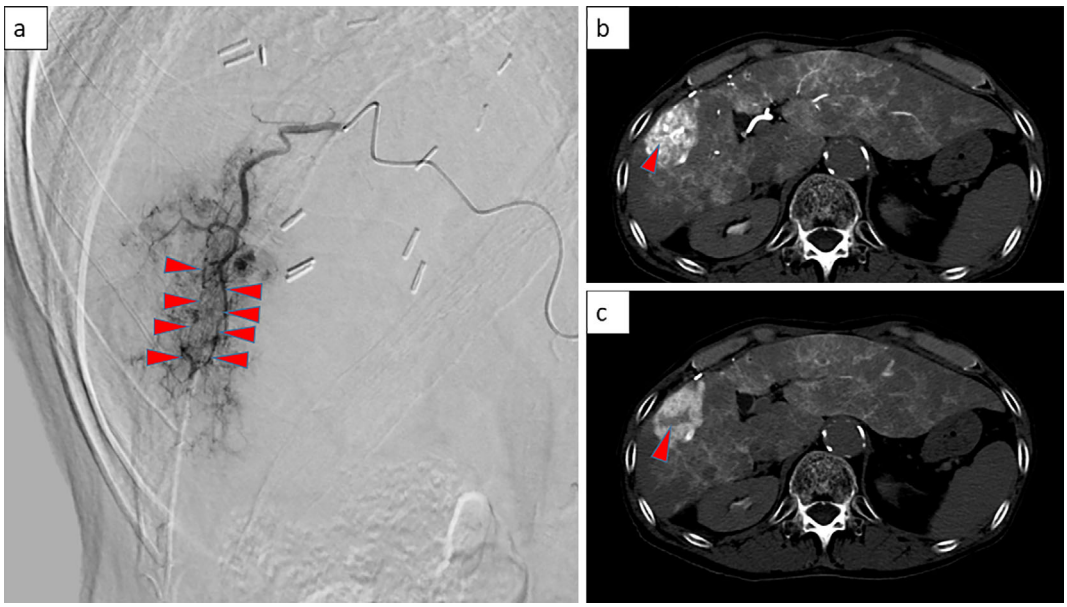

Figure 2. (a) Hepatic angiography showing the thread and streaks sign, which implies a vascularized tumor thrombus (red arrowhead). (b) CT hepatic arteriography in the early phase showing multinodular recurrence of HCC with PVTT. A mass with ill-defined enhancement involving the P5 branch (red arrowhead). (c) CT hepatic arteriography showing PVTT on the P5 branch washed out in the delayed phase (red arrowhead). CT: computed tomography, HCC: hepatocellular carcinoma, PVTT: portal vein tumor thrombus

Table 1. Laboratory Investigations.

Variables	Value	Unit	Variables	Value	Unit	Variables	Value	Unit
RBC	264	$\times 10^4/\mu L$	CRP	0.13	mg/dL	Na	138	mEq/L
Hb	8.8	%	TP	7.5	g/dL	K	4.5	mEq/L
WBC	3,590	/μL	Albumin	3.4	g/dL	Cl	104	mEq/L
Neut	68.1	%	ChE	131	IU/L	Ca	8.8	mg/dL
Eos	0.9	%	T-BIL	0.37	mg/dL			
Baso	0.1	%	AST	29	IU/L	PT	69	%
Lymph	25.1	%	ALT	14	IU/L			
Mono	5.9	%	LDH	221	IU/L	CEA	2.31	ng/mL
PLT	9	$\times 10^4/\mu L$	ALP	187	IU/L	DCP	95	mAU/mL
			γ-GTP	26	IU/L	AFP	955	ng/mL
			UA	4.2	mg/dL	AFP-L3	75.1	%
			Creatinine	0.71	mg/dL	CA19-9	21.5	ng/mL
			BUN	14.9	mg/dL			

RBC: red blood cell, Hb: hemoglobin, WBC: white blood cell, Neut: neutrophils, Eos: eosinophils, Baso: basophils, Lymph: lymphocytes, Mono: monocytes, PLT: platelet, CRP: C reactive protein, TP: total protein, Ch-E: cholinesterase, T-BIL: total-bilirubin, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, γ-GTP: γ-glutamyl transpeptidase, UA: uric acid, BUN: blood urea nitrogen, PT: prothrombin time, CEA: carcinoembryonic antigen, DCP: des-γ-carboxy prothrombin, AFP: alfa-fetoprotein, AFP-L3: AFP lectin fraction, CA19-9: carbohydrate antigen 19-9

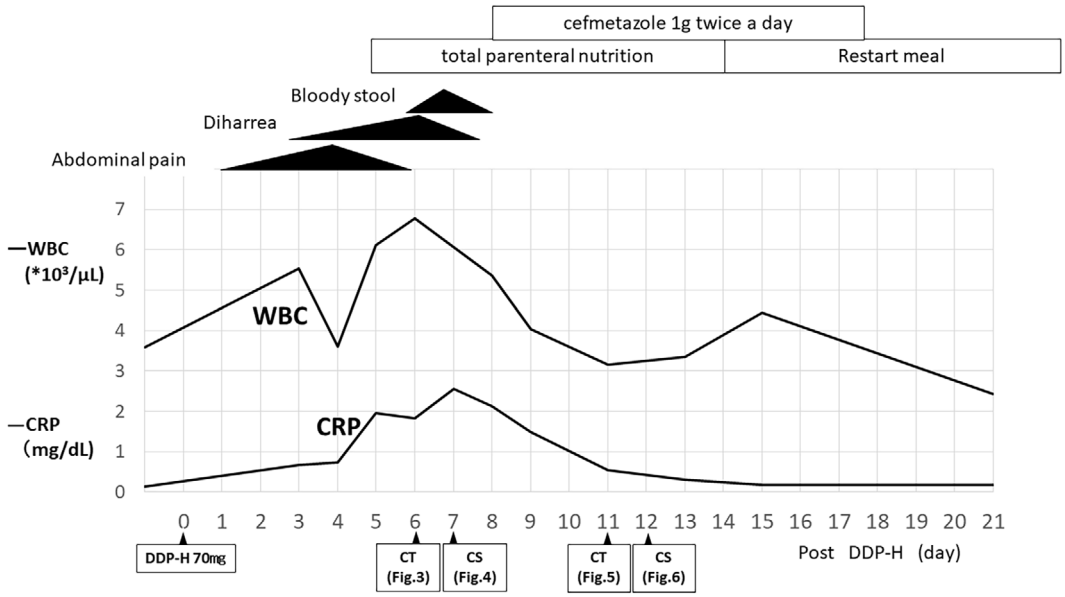

Figure 3. The clinical course of the patient described in the present case report.

and was administered cefmetazole at a dose of 1 g twice a day to prevent bacterial translocation. He showed gradual improvement in symptoms and laboratory test parameters. CT performed on the 11th day revealed significant improvement in edematous mucosa between the transverse colon and the rectum. However, gastric wall thickening partially remained (Fig. 6). Colonoscopy performed on the 12th day also revealed improvement in the reddish edematous mucosa and the vascular pattern (Fig. 7). A histopathological examination of colonic biopsy specimens obtained from erosions showed lymphocytic infiltration and foamy histiocytes in the lamina propria; however, these findings could not confirm the cause of colitis. Oral intake was resumed on the 13th day, and his symptoms did not recur.

Discussion

To our knowledge, this is the first case report that describes severe colitis secondary to the administration of HAIC with cisplatin. Although colitis was successfully treated conservatively with TPN for bowel rest, the edematous colonic mucosa throughout the colon and slightly blood-stained stool required close attention in this patient.

Advancements in chemotherapeutic regimens over the last decade have led to the use of several anticancer agents for HCC. HCC treatment guidelines proposed by the American

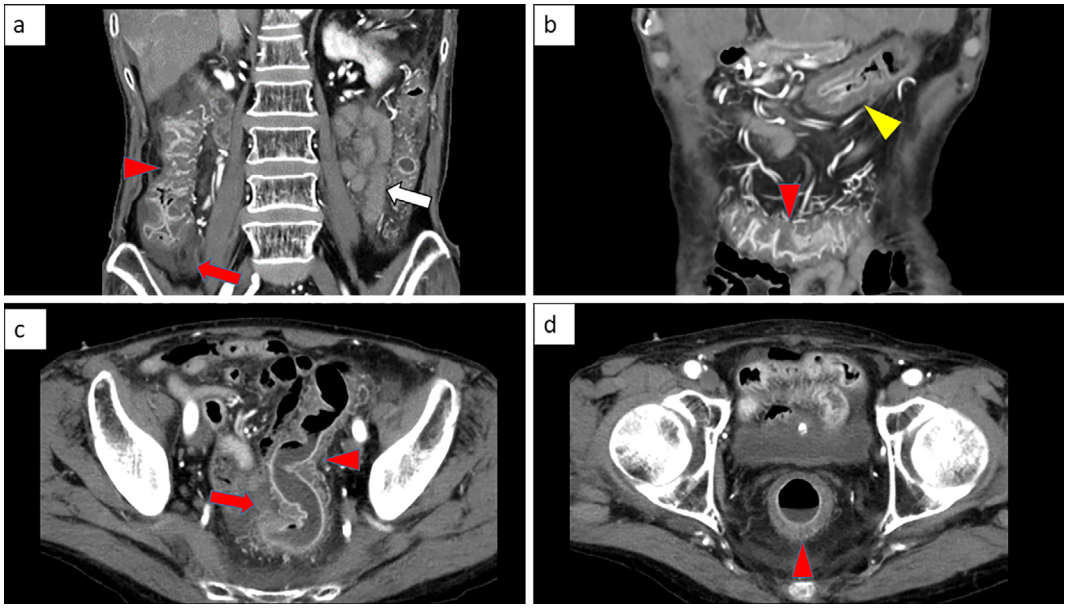

Figure 4. **CECT showing significant bowel wall thickening between the cecum and the rectum (red arrowhead) without contrast failure or vascular thrombosis and also showing gastric wall thickening (yellow arrowhead). The small bowel wall did not show thickening (white arrowhead). Fat stranding is observed around the cecum and the sigmoid colon (red arrow). CECT: contrast-enhanced computed tomography**

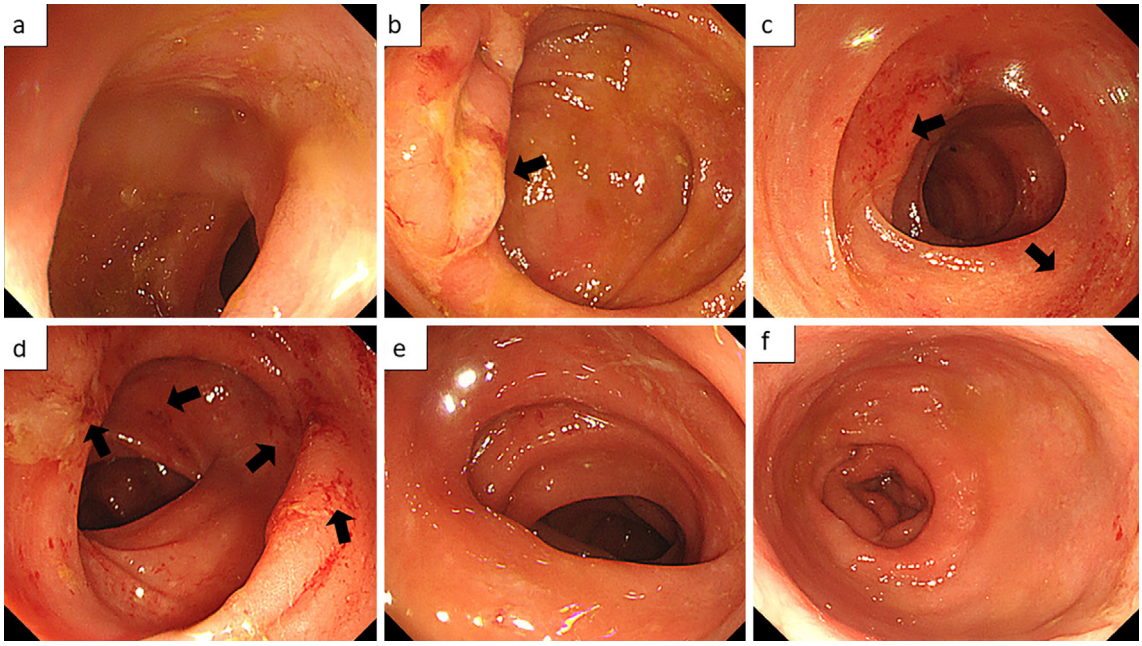

Figure 5. **Colonoscopic images showing reddish edematous mucosa with a reduced vascular pattern throughout the colon in the following segments: (a) the terminal ileum, (b) cecum, (c) transverse colon, (d) descending colon, (e) sigmoid colon, and (f) the rectum. Multiple slight erosions can be observed (arrow).**

Association for the Study of Liver Diseases and the European Association for the Study of the Liver recommend molecular-targeted therapy to treat advanced HCC (11, 12); however, HAIC is also used in Asia as one of the most effective treatment strategies for advanced HCC, particularly in patients with portal vein invasion (13). Based on the Japanese Clinical Practice Guidelines for HCC, HAIC and molecular-targeted therapy are considered second-line treatments following TACE for advanced intrahepatic HCC (14). In Japan, IA-call® (a platinum-based anticancer drug) is often used for HAIC in patients with TACE-refractory HCC (9, 10). The cisplatin dosage administered is the pri-

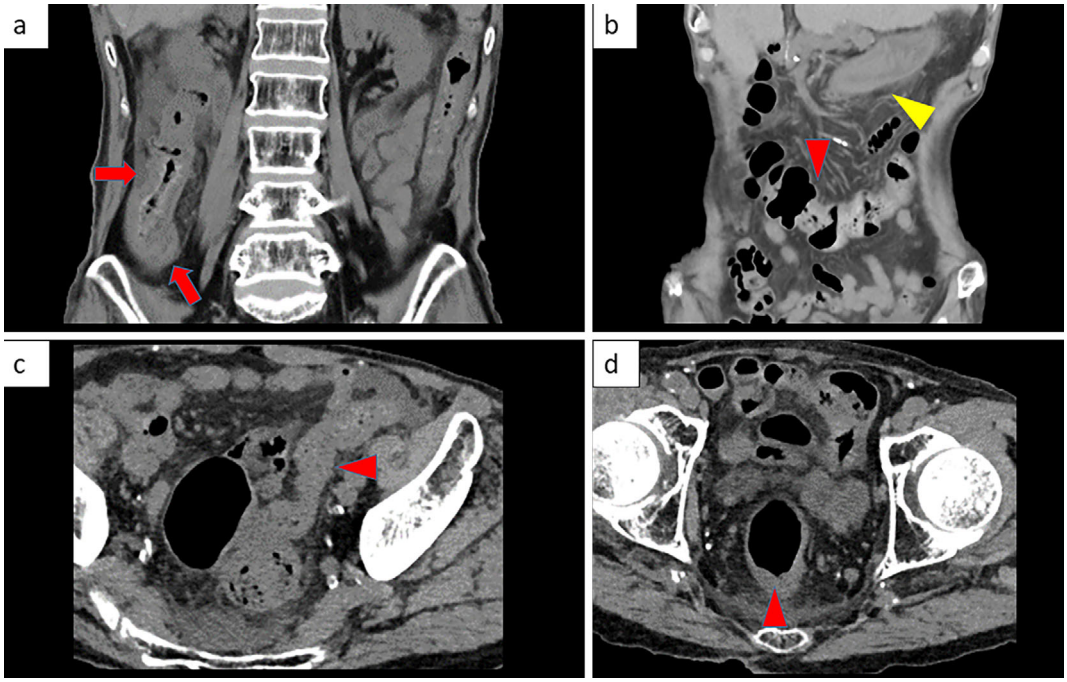

Figure 6. **(a) Residual bowel wall thickening and slight fat stranding are observed around the ascending colon (arrow). (b-d) CT images showing significant improvement in the edematous mucosa between the transverse colon and the rectum (arrowhead). Gastric wall thickening partially remained (yellow arrowhead). CT: computed tomography**

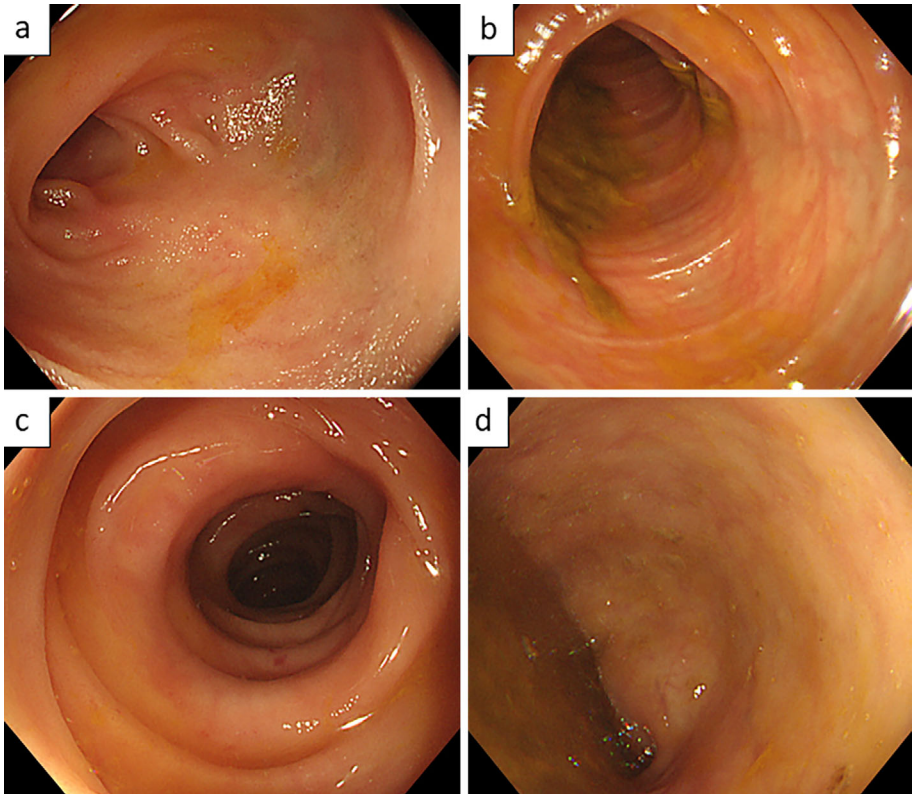

Figure 7. **Colonoscopic images showing improvement in the reddish edematous mucosa and the vascular pattern throughout the colon.**

mary factor affecting the development and the severity of adverse effects. The most common adverse effects of cisplatin used for HAIC are renal toxicity and cytopenia (15, 16). Although general chemotherapy with cisplatin is known to occasionally cause colitis (particularly neutropenic colitis) (6, 8), no report has described colitis

Table 2. Summary of Previous Literature.

Reference	Age	Sex	Primary tumor	Drug	Route	Timing	Ischemic change	Neutropenia	Diagnose	Treatment	Outcome
3)	71	male	bile-duct cancer	GEM+CDDP	div	2 days	yes	no	ischemic colitis	surgery	death
4)	72	male	salivary gland carcinoma	DTX+CDDP	IA	2 days	yes	yes	ischemic colitis	TPN	improved
4)	51	male	salivary gland carcinoma	DTX+CDDP	IA	unknown	no	no	mucositis	observe	improved
5)	45	male	gastric cancer	CAPE+CDDP	div	28 days	yes	no	ischemic colitis	observe	death
6)	73	male	SCLC	IRI+CDDP	div	13 days	no	yes	neutropenic colitis	observe	improved
7)	58	female	gastric cancer	DTX+CDDP+5FU	div	54 days	no	no	cecal perforation	surgery	improved
8)	60	male	head and neck cancer	5FU+CDDP	div	7 days	unknown	yes	neutropenic colitis	observe	improved

DTX: docetaxel, CDDP: cisplatin, 5-FU: Fluorouracil, IRI: irinotecan, GEM: gemcitabine, CAPE: capecitabine, div: drip infusion in vein, IA: intra arterial infusion

secondary to HAIC with cisplatin because the dosage of cisplatin used for HAIC is relatively small.

Chemotherapy-induced gastrointestinal is a common complication observed in patients with cancer. Neutropenic enterocolitis, ischemic colitis, and pseudomembranous colitis are the specific types of colitis that occur as adverse effects of chemotherapy. Neutropenic colitis occurs in any patient with significant neutropenia, which commonly occurs during the third week after receiving cytotoxic chemotherapy (6, 8, 17). Ischemic colitis has been reported with the administration of docetaxel- or gemcitabine-containing regimens, which manifests as blood-stained stool and intestinal necrosis on a colonoscopic examination (3-5). Although pseudomembranous colitis is a well-known complication of antibiotic treatment, it is also a common complication in patients with cancer (18). In our case, the colonoscopic findings, which revealed edematous reddish mucosa without intestinal necrosis and pseudomembrane formation, were not consistent with ischemic or pseudomembranous colitis. Additionally, laboratory tests for *C. difficile* toxin revealed negative results, which excluded pseudomembranous colitis in this patient. Although a previous study reported that combination therapy using 5-fluorouracil (5FU) and cisplatin caused neutropenic colitis in a patient with head and neck cancer, neutropenia was not observed after the administration of cisplatin in our patient, so neutropenic colitis was also ruled out.

In our case, clopidogrel and low-dose aspirin, which the patient had been taking, may have contributed to the blood-stained stool due to the colitis. In fact, these drugs can sometimes cause colon mucosal disorders (19). However, the immediate improvement and lack of recurrence of colitis after short-term cessation of clopidogrel did not correspond with the clinical course of colitis caused by these drugs.

Intestinal mucositis is a common adverse effect in patients with cancer undergoing combination chemotherapy using 5 FU and irinotecan. Irinotecan and 5FU cause acute injury to the intestinal mucosa, which is a dose-limiting complication resulting in loss of epithelium (1, 2). A study performed by Cappell et al., which described colonic toxicity secondary to administered drugs and chemicals, reported that 5-FU caused allergic and inflammatory colitis (20). In our case, both the improvement in the colonoscopic findings of edematous reddish mucosa as well as the immediate symptomatic improvement in the patient implicated allergic colitis as a possible etiopathogenetic contributor. Notably, cisplatin was not mentioned as a possible cause of allergic colitis in the study of Cappell et al., and no previous reports have implicated cisplatin as a possible cause of allergic colitis either.

We performed DLST for cisplatin to differentiate the allergic pathway; however, the test showed a negative result. Notably, Pichler et al. reported that a negative result with DLST could not exclude drug hypersensitivity because the DLST shows limited sensitivity (21). Therefore, we were unable to exclude the possibility of allergic colitis caused by cisplatin. In addition, the appearance and immediate improvement of gastric wall thickening concurrent with colitis sustained this allergic pathway. Unfortunately, we performed only colonoscopy and two biopsies from the rectum, and too few eosinophils were observed to allow for the determination of an allergic reaction. It is difficult to diagnose an allergic reaction by a biopsy because eosinophils are present even in normal physiologic states throughout the gastrointestinal tract. With respect to eosinophilic gastroenteritis, some studies have recommended multiple biopsies - at least four to five biopsies per site - from several sites, such as the stomach and small bowel mucosa (22, 23). The discrepancy in the concentration of eosinophils between each part of the gastrointestinal mucosa must also be investigated. For the colon, Turner et al. reported that the concentration of eosinophils was higher in the right colon than in the left colon (24). Therefore, multiple biopsies from different parts of the colon are needed. Furthermore, gastroendoscopy and/or enteroscopy should have been performed to confirm thicken-

ing of the gastric wall and small bowel wall, as we were unable to assess these sufficiently.

Table 2 shows the previous reports that have discussed chemotherapy-induced colitis, including those describing the use of cisplatin. Although early-onset colitis occurred in two previous patients, as well as in our patient two days after the administration of chemotherapy, ischemic mucosal changes in the colon were reported in these previous cases. Among the three patients with ischemic colitis that was attributed to the administration of docetaxel, gemcitabine and capecitabine, two showed a poor prognosis. Two cases of neutropenic colitis were reported in patients who received doublet chemotherapy. No reports have described severe colitis in patients who received chemotherapy with only cisplatin. Furthermore, allergic colitis without ischemia and neutropenia (as was observed in our patient) has never been reported.

In conclusion, HAIC with cisplatin alone for HCC caused severe colitis in the patient described in this report. Although the cause of this colitis could not be accurately identified, an allergic response was implicated as the most likely pathomechanism. Conservative treatment with TPN effectively treated the colitis in our patient. We emphasize that physicians should consider the possibility of colitis as an adverse effect of cisplatin administration for the prompt diagnosis and prevention of aggravation of colitis.

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

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