Non-obstructive mesenteric ischaemia during drug therapy for maxillary cancer: A case report

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Received February 7, 2024; Accepted June 25, 2024

DOI: 10.3892/br.2024.1860

Abstract. Non-occlusive mesenteric ischaemia (NOMI) refers to irreversible intestinal ischaemia and necrosis in the absence of organic obstruction to the mesenteric blood vessels. In cases of delayed diagnosis, the prognosis is poor and the mortality rate is 58-70%, being the highest among patients with acute mesenteric ischaemia. The risk factors for this disease include heart disease, sepsis, and administration of catecholamines and digitalis; however, there are few reports of its onset during drug therapy for malignant tumours. The present study reported the case of an 85-year-old man who developed NOMI during drug therapy for maxillary cancer. The patient was diagnosed with right maxillary carcinoma, for which paclitaxel, carboplatin and cetuximab (PCE) therapy was administered. Four days after starting the second course of PCE therapy, the patient visited the emergency department of our hospital with chief complaints of melena and abdominal pain. Contrast-enhanced computed tomography revealed ischaemia from the transverse to the descending colon, leading to a diagnosis of NOMI. Colectomy and colostomy were performed during the emergency surgery on the same day. Although the patient's general condition improved, he was transferred to a recuperation facility for palliative care.

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Abbreviations: NOMI, non-occlusive mesenteric ischaemia; PCE, paclitaxel, carboplatin and cetuximab; PTX, paclitaxel; 5-FU, 5-fluorouracil; CT, computed tomography; AMI, acute mesenteric ischaemia

Key words: non-occlusive mesenteric ischaemia, drug therapy, oral cancer, squamous cell carcinoma, paclitaxel

Introduction

Non-occlusive mesenteric ischaemia (NOMI) refers to irreversible intestinal ischemia and necrosis in the absence of organic obstruction of the mesenteric blood vessels. In cases of delayed diagnosis, the prognosis is poor and the mortality rate is 58-70%, being the highest among those with acute mesenteric ischaemia (AMI) (1). The risk factors for this condition include heart disease, sepsis and the use of catecholamines and digitalis (2). The onset mechanism of NOMI involves a reduction in intestinal blood flow due to factors such as decreased cardiac output, reduced circulating blood volume, mesenteric contraction, mesenteric vasospasm caused by sepsis or the use of vasoconstrictive therapeutic agents. This pathological condition leads to diminished intestinal blood flow, ultimately resulting in intestinal ischaemia (3,4). In the early stages of onset, 20-30% of the patients do not complain of abdominal pain. When abdominal pain does occur, its location and severity can vary widely. However, as ischaemia progresses, patients typically develop persistent abdominal pain, melena and flatulence. With further disease progression, symptoms of peritoneal irritation, such as muscular guarding and Blumberg's sign, become evident (2,5). Treatment with vasodilators is considered useful if there is no intestinal necrosis; however, surgery is required if the intestinal tract has reached an irreversible ischaemic state (2,5,6). Therefore, early diagnosis of intestinal necrosis, which indicates the need for surgery, is crucial. NOMI can manifest as a shock and can be fatal, requiring immediate surgical treatment (2). The current study reported a case in which early diagnosis of NOMI allowed for emergency surgery, ultimately saving the patient's life.

Case report

The patient first presented at Toyama University Hospital (Toyama, Japan) in January 2022 with the chief complaint of a painful tumour in the right cheek without an ulcer. The tumour was elastic, firm and immobile, measuring 65x50 mm. Right maxillary carcinoma (cT4bN1M0) was confirmed according to imaging and histopathological examinations. The patient's medical history included cerebral haemorrhage (left paresis),

early gastric cancer, colon polyps, hypertension and dementia. Since the tumour was deemed unresectable, paclitaxel, carboplatin and cetuximab (PCE) was administered as induction drug therapy. Although drug therapy was successful and CT revealed the lesion was observed to shrink after the first course of PCE therapy, the patient visited the emergency department of our hospital with chief complaints of melena and abdominal pain 4 days after day 1 of the second course of PCE therapy. Upon transportation to our hospital, the patient's Glasgow Coma Scale level of consciousness was E4V4M6 (Score: 14, mild) (7), oxygen saturation was 90% (normal range, 96-99% under room air), blood pressure was 92/52 mmHg (normal value, 140/90 mmHg) and the heart rate was 111 bpm (normal range, 60-100 bpm); furthermore, the patient experienced a peripheral cold sensation. In addition, the abdomen was flat, elastic and soft with no tenderness, and blood gas analysis revealed pH of 7.385 (normal range, 7.35-7.45) and lactic acid level of 4.8 mmol/l (normal range, 0.5-1.6 mmol/l). Based on these findings, the patient was diagnosed with circulatory failure due to bleeding. Lower gastrointestinal endoscopy, performed to investigate the bleeding points, revealed oedema and dark purple discoloration of the intestinal mucosa, as well as a large amount of faeces in the rectum (Fig. 1). Acute intestinal ischaemia was diagnosed and contrast-enhanced CT was performed to check for arterial occlusion due to the thrombus. Although the images showed ischaemia from the transverse to descending colon (Fig. 2), no thrombus was found in the superior mesenteric artery. At that time, the abdomen was slightly hard and tender. Based on these findings, the patient was diagnosed with NOMI. Emergency surgery, including colectomy (from the sigmoid colon to the sigmoid rectum) and colostomy augmentation, was performed on the same day. The resected specimen showed full-thickness necrosis of the sigmoid rectum (Fig. 3). Histopathological examination performed according to standard procedures showed massive necrosis of the colon and proliferation of neutrophils. No thrombi were observed in the blood vessels directly beneath the necrotic mucosa, and the lumen remained patent (Fig. 4). Thereafter, the patient's general condition improved and no further increase of the lesion in the right maxillary region was observed. However, owing to a decline in cognitive function and the presence of aspiration pneumonia, the patient's performance status (8) decreased from 2 to 3 and he was transferred to a recuperation facility for palliative care. The patient's subsequent progress is unknown.

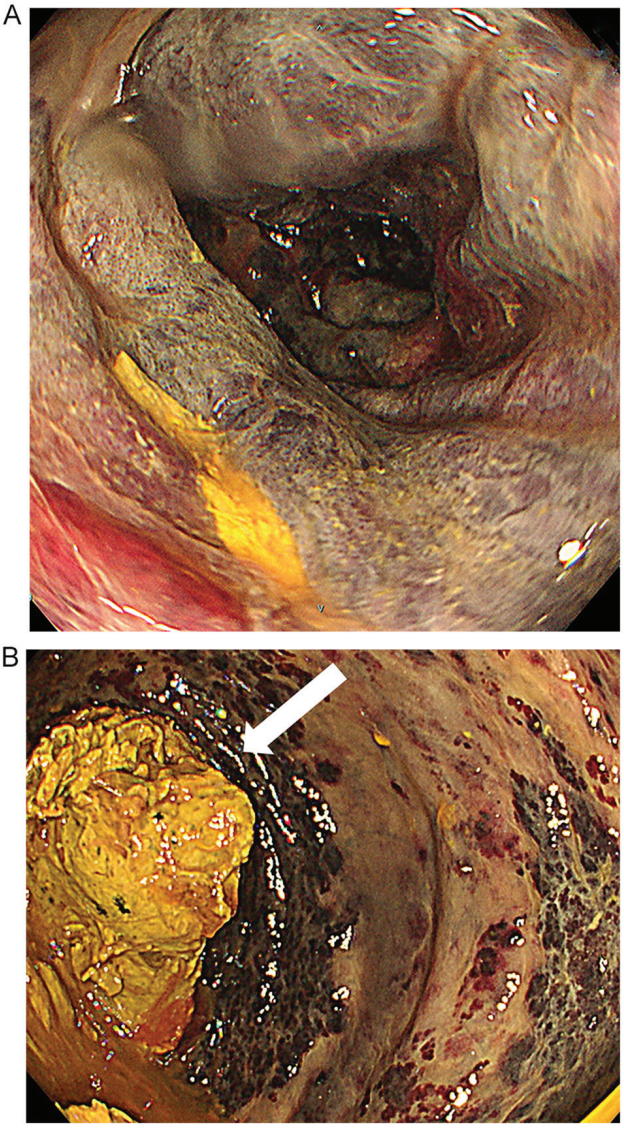

Figure 1. Lower gastrointestinal endoscopy findings. (A) Oedema and dark purple changes in the intestinal mucosa are observed. (B) A large amount of stool (arrow) is found in the rectum.

Discussion

NOMI was first reported in 1958 by Ende (9) in a patient with intestinal necrosis and heart failure. NOMI is known to cause ischaemia or necrosis of the intestinal tract, despite the absence of organic obstruction of the main mesenteric blood vessels. Heer *et al* (10) defined NOMI as follows: i) No obstruction in the mesenteric arteries and veins in areas of intestinal necrosis; ii) discontinuous necrosis and ischaemic changes in the intestinal tract; and iii) histopathological findings showing the presence of bleeding and necrosis. However, it is defined by the lack of fibrin thrombus in the venules (10). The onset mechanism of NOMI involves a reduction in intestinal blood flow due to factors such as decreased cardiac output, reduced circulating blood volume, mesenteric contraction and mesenteric vasospasm caused by sepsis or the use of vasoconstrictive therapeutic agents. This pathological condition leads to diminished intestinal blood flow, ultimately resulting in intestinal ischaemia (3,4). Furthermore, rapid acceleration of intestinal peristalsis and an increase in intestinal pressure caused by faecal impaction or enema has been reported to cause intestinal ischaemia (11). The risk factors for NOMI include cardiovascular disease, myocardial infarction, sepsis, arrhythmia and the use of catecholamines or digitalis (2). A search in PubMed (https://pubmed.ncbi.nlm.nih.gov) and J-stage (https://www.jstage.jst.go.jp) for the search terms (NOMI and chemotherapy) retrieved reports of only 15 cases of NOMI due to chemotherapy (Table I) (5,12-21). The reason why most of the reported cases are Japanese is unclear and further investigation is needed. Docetaxel was used in six cases, paclitaxel in three cases and taxane-based anticancer drugs were used in nine cases. The onset of

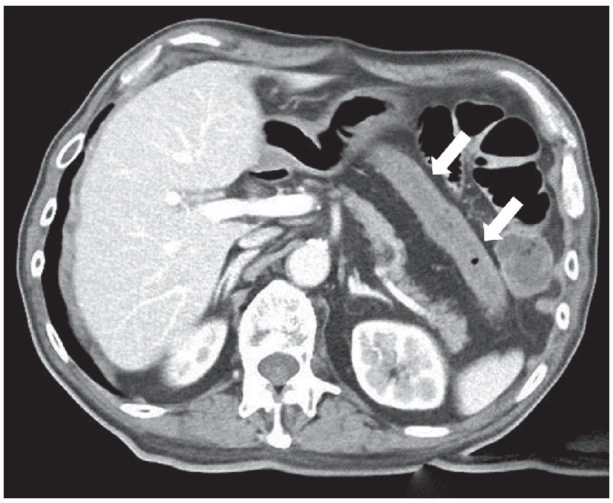

Figure 2. Abdominal contrast-enhanced computed tomography findings. Ischaemia was observed from the transverse colon to the descending colon (arrows).

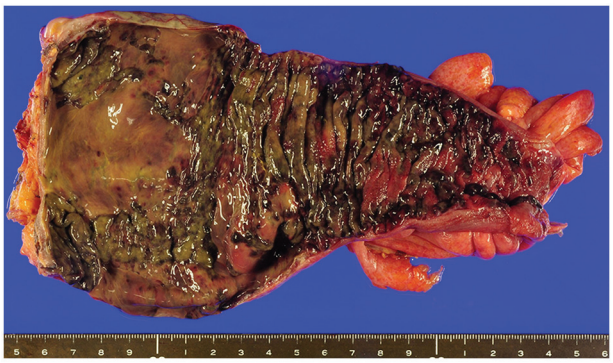

Figure 3. Resected sigmoid rectum. Full-thickness necrosis of the sigmoid rectum was observed.

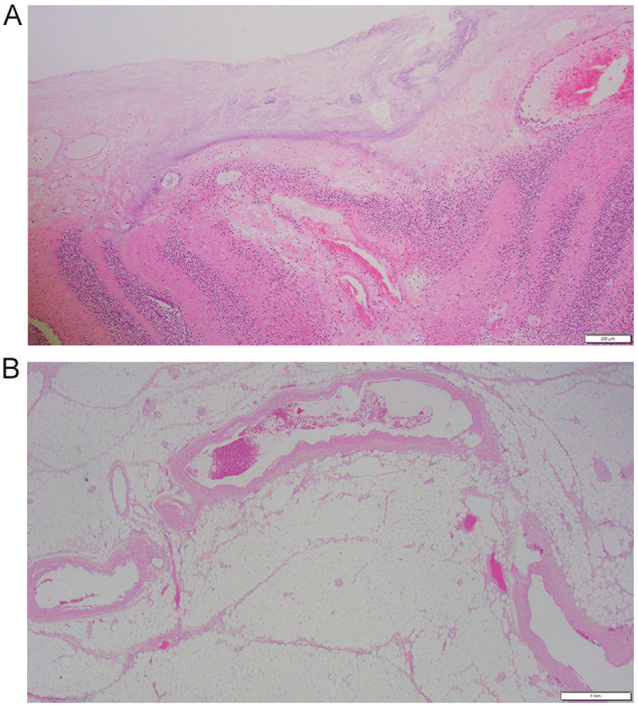

Figure 4. Histopathological findings of the specimen. (A) Massive necrosis of the colon and proliferation of neutrophils were observed (magnification, x40; scale bar, 200 μm; haematoxylin and eosin stain). (B) No thrombi were observed in the blood vessels directly beneath the necrotic mucosa, and the lumen remained patent (magnification, x12.5; scale bar, 1 mm; haematoxylin and eosin stain).

NOMI after chemotherapy has been linked to several factors: Mucosal damage due to the inhibition of epithelial cell division and proliferation, a pharmacological effect of taxane-based anticancer drugs (22); and vascular system damage resulting from the inhibition of vascular smooth muscle cell proliferation and migration and neointimal accumulation (23). The intestinal mucosa repeatedly regenerates every 3rd to 4th day and intestinal mucosal damage appears after the 3rd to 4th day of administration due to the suppression of intestinal epithelial cell division and proliferation by taxane-based anticancer drugs. The increased intestinal pressure caused by chemotherapy-induced constipation contributes to the onset of NOMI (5). Taxane-based anticancer drugs have been approved for use against a wide range of malignant tumours, including ovarian, breast and head and neck cancers. Intestinal disorders such as gastrointestinal necrosis, perforation, bleeding, ulcers and severe enteritis have been reported, although at a low incidence (<0.1%) (24). However, in the case of ischaemic colitis due to taxane-based anticancer drugs, drug discontinuation has been found to ameliorate the symptoms; in such cases, the causative drug should not be re-administered (25). Seewaldt *et al* (26) reported that paclitaxel-induced intestinal necrosis is caused not only by toxicity to the intestinal epithelium, but also by a history of laparotomy, cancer progression, intraperitoneal radiotherapy and chemotherapy. Intestinal necrosis occurs because of the effects of paclitaxel on the intestinal epithelium in the intestinal tract, where mucosal damage occurs. In the present case, the patient had a history of surgery for colonic polyps and the necrotic segment of the colon that was resected was the same segment previously containing the polyps. Therefore, intestinal mucosal damage had already occurred. In this case, the administration of anticancer drugs was thought to be the cause of intestinal necrosis. Furthermore, lower gastrointestinal endoscopy revealed a large amount of stool, and increased intestinal pressure owing to constipation was considered a contributing factor to the onset of NOMI. In cases of delayed diagnosis, the prognosis is poor, with a mortality rate of 58-70%, being the highest for those with AMI (1). The underlying reason for this is the lack of distinctive clinical symptoms, leading to a delayed diagnosis (27). In the early stages of onset, 20-30% of the patients do not complain of abdominal pain. When abdominal pain does occur, its location and severity can vary widely. However, as ischaemia progresses, patients typically develop persistent abdominal pain, melena and flatulence. With further disease progression, symptoms of peritoneal irritation, such as muscular guarding and Blumberg's sign, become evident (2,5). Blood tests show elevated levels of C-reactive protein, aspartate aminotransferase, alanine aminotransferase, creatine phosphokinase, lactate dehydrogenase and lactate, as well as metabolic acidosis, but these are

Table I. Previously reported cases of non-occlusive mesenteric ischaemia during drug therapy.

Author(s), year	Age, years/sex	Cancer type	Drug therapy regimen	Outcome	(Refs.)
Pearson *et al*, 2008	53/female	Metastatic liver cancer	CDDP, ADM MMC	Survival	(12)
Yoshida *et al*, 2020	63/female	Oropharyngeal cancer	DOC, CDDP, 5-FU	Death	(5)
Yoshida *et al*, 2020	71/male	Oropharyngeal cancer	DOC, CDDP, 5-FU	Death	(5)
Tanaka *et al*, 2018	74/male	Oropharyngeal cancer	DOC, CDDP, 5-FU	Survival	(13)
Wada *et al*, 2017	79/male	Prostate cancer	DOC	Survival	(14)
Wada *et al*, 2017	74/male	Oropharynx cancer	DOC, CDDP, 5-FU	Survival	(14)
Ikeda *et al*, 2007	84/female	Breast cancer	PTX	Survival	(15)
Awano *et al*, 2013	80/female	Lung adenocarcinoma	Gefitinib	Death	(16)
Matsuzawa *et al*, 2015	74/female	Melanoma	PTX, CBDCA	Survival	(17)
Yamane *et al*, 2015	68/male	Small cell lung cancer	CDDP, ETP	Survival	(18)
Nagano *et al*, 2021	74/male	Oropharyngeal cancer	S-1 (+ radiation)	Death	(19)
Nagano *et al*, 2021	69/male	Oropharyngeal cancer	DOC, CDDP, 5-FU	Death	(19)
Kuwayama *et al*, 2022	58/male	Hodgkin lymphoma	Nivolumab	Survival	(20)
Oikawa *et al*, 2022	76/male	Glioblastoma	Bevacizumab	Death	(21)
Present case, 2024	85/male	Maxillary cancer	PTX, CBDCA, Cmab	Survival	-

ADM, adriamycin; MMC, mitomycin C; CBDCA, carboplatin; PTX, paclitaxel; Cmab, cetuximab; DOC, docetaxel; CDDP, cisplatin; 5-FU, fluorouracil; ETP, etoposide.

not specific to the diagnosis of NOMI (2). The usefulness of CT in the diagnosis of NOMI has been reported (29). In the past, diagnosis with CT was considered difficult, but in recent years, advances in multidetector-CT have improved the ability to visualise blood flow in the blood vessels, intestines and mesentery, thereby improving the diagnostic performance. Contrast-enhanced CT is essential for diagnosis, and findings, such as decreased or absent contrast effects on the intestinal wall, which are signs of intestinal ischaemia, can be observed. In the present case, NOMI was suspected and additional contrast-enhanced CT revealed ischaemia from the transverse colon to the descending colon. Treatment with vasodilators is considered useful if there is no intestinal necrosis; however, surgery is required if the intestinal tract has reached an irreversible ischaemic state (2,5,6). Therefore, early diagnosis of intestinal necrosis, which indicates the need for surgery, is crucial. NOMI can manifest as a shock and can be fatal, requiring immediate surgical treatment (2). If abdominal symptoms such as abdominal pain and vomiting occur during drug therapy, intestinal ischaemia should be suspected and discontinuation of anticancer drugs should be considered.

In conclusion, if a patient has a history of abdominal surgery or evidence of intestinal mucosal disorders (such as constipation), early imaging examinations (including contrast-enhanced CT) and consultation with a gastroenterologist should be considered to rule out NOMI.

Acknowledgements

The authors express their great appreciation to Professor Kenichi Hirabayashi (Department of Diagnostic Pathology, Faculty of Medicine, University of Toyama, Toyoma, Japan) and Dr Takashi Minamisaka (Department of Diagnostic Pathology, Toyama University Hospital, Toyoma, Japan) for histopathological analysis.

Funding

No funding was received.

Availability of data and materials

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

Authors' contributions

AI, RI, KS, DT, MT and SY treated the patient with PCE. AI, KS and KF performed the follow-up. AI, SY, RI and MN drafted the manuscript. AI, RI, SY and MN prepared the figures and table. AI, SY and MN confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Written informed consent was obtained from the patient for the publication of this case report and the accompanying images.

Competing interests

The authors declare that they have no competing interests.

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