〈Case Report〉

A case of synchronous triple cancer of the esophagus, stomach, and colon detected by using gastrointestinal screening endoscopy

Takahisa MURAO [1)], Tomoari KAMADA [2)], Aya SUNAGO [2)]
Ryo KATSUMATA [3)], Mitsuhiko SUEHIRO [3)], Noriaki MANABE [4)]
Tomoki YAMATSUJI [5)], Yasumasa MONOBE [6)], Hiroshi NAGAI [7)]
Toshihiro TAKAO [2)], Akiko SHIOTANI [1)], Ken HARUMA [3)]

1) Division of Gastroenterology, Department of Internal Medicine,
2) Department of Health Care Medicine,
3) Department of General Internal Medicine 2,
4) Department of Endoscopy and Ultrasound,
5) Department of General Surgery,
6) Department of Pathology, Kawasaki Medical School
7) Nagai Medical Clinic

ABSTRACT In recent years, the detected number of multiple primary malignant tumors (MPMTs) in the gastrointestinal tract has been increasing with the advancement of gastrointestinal endoscopic equipment and the spread of endoscopic screening.

Here, we report a case of synchronous MPMTs of the esophagus, stomach, and colon detected by means of gastrointestinal screening endoscopy. The patient was a 67-year-old man who regularly visited the medical clinic for hypertension. He had a history of alcohol consumption (sake index: 250, with alcohol flushing syndrome) and smoking (Brinkman index: 800), and a family history of cancer (his father had gastric cancer).

At the medical clinic, he underwent gastrointestinal endoscopy for screening purposes. Prior observation with linked-color imaging (LCI), a type of image-enhanced endoscopy (IEE), revealed an irregular depressed lesion in the mid-esophagus. Simultaneously, an irregular, highly deformed depressed lesion and a small depressed lesion were detected on the incisura of the lesser curvature and the lesser curvature of the antrum, respectively. The esophageal lesion was identified as squamous cell carcinoma and both gastric lesions were identified as well-differentiated adenocarcinoma.

The patient was referred to our hospital for further examination and treatment for esophageal and gastric cancer. Subsequent colonoscopy revealed a well-defined, ulcerative tumor in the

Corresponding author
Tomoari Kamada
Department of Health Care Medicine, Kawasaki Medical School, Kawasaki Medical School General Medical Center, 2-6-1 Nakasange, Kita-Ku, Okayama, 700-8505, Japan
Phone : 81 86 225 2111
Fax : 81 86 232 8343
E-mail: tkamada@med.kawasaki-m.ac.jp

transverse colon. First, endoscopic submucosal dissection was performed for the esophageal lesion, followed by laparoscopy-assisted distal gastrectomy with D1+ lymph-node dissection and transverse colectomy with D2 lymph-node dissection for the gastric and colorectal lesions, respectively. Histopathologically, the main gastric and colonic tumors were in advanced stages; fortunately, the esophageal cancer was an early-stage lesion (7 × 5 mm, 0-IIc, pT1a-LPM, INFa, ly0, v0, pCurA), which has a much better prognosis than advanced esophageal cancer.

In patients with multiple cancer risk factors (alcohol consumption, smoking, and family history), it is important to consider the possibility of MPMTs. Furthermore, upper gastrointestinal observation combined with IEE, such as LCI, may be useful in the early detection of lesions.

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Key words：Esophageal cancer, Image-enhanced endoscopy, Gastrointestinal screening endoscopy, Linked color imaging, Synchronous triple cancers

INTRODUCTION

With the development of tumor diagnostic technology, the incidence of multiple primary malignant tumors (MPMTs) has increased greatly[1−3]. There are two types of MPMTs: synchronous and metachronous. The former may be defined as a second primary malignancy diagnosed within 6 months of the diagnosis of the first primary malignancy, while the latter refers to a second primary malignancy diagnosed more than 6 months after the first primary malignancy[2].

Narrow-band optical methods used in image-enhanced endoscopy (IEE) include narrow-band imaging (NBI), blue-laser imaging (BLI), and linked-color imaging (LCI), all of which make use of irradiated light of a specific wavelength. Recently, IEE was reported as being more effective than white-light imaging (WLI) for the early detection of upper gastrointestinal tumors[4−11].

Here, we report a case of triple cancer in which early-stage esophageal cancer was treated with endoscopic submucosal dissection (ESD) and simultaneous multiple gastric cancers and colon cancer were treated surgically.

CASE REPORT

[Patient] A 67-year-old man.

[Chief complaint] None.

[Past illness] None.

[Family history] Gastric cancer (the patient's father).

[History of alcohol consumption] Sake index: 250, alcohol flushing syndrome.

[Smoking history] Brinkman index: 800.

[Medical history] Treated for hypertension with a single medication to date at a medical clinic.

[Present illness] In November 2020 the patient underwent gastrointestinal endoscopy for the first time at a local medical clinic, upon which one lesion was observed in the esophagus and two in the stomach. That in the esophagus was diagnosed as squamous cell carcinoma (SCC) and those in the stomach were both diagnosed as well-differentiated adenocarcinoma. In January of the following year, he was referred to our hospital for further investigation and treatment. He underwent a colonoscopy at our hospital for preoperative screening purposes.

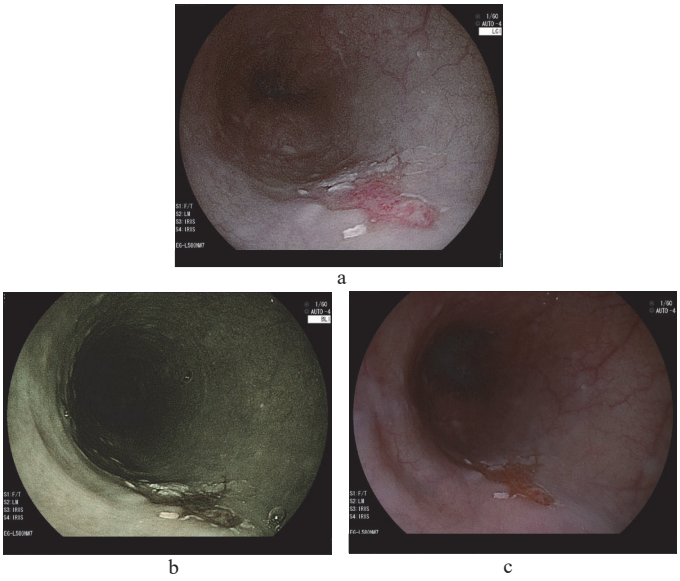
[Physical findings] Height: 163 cm, weight: 53.5 kg (BMI: 20.1 kg/m^2). No anemia was detected upon investigation of the palpebral conjunctiva, there was no abnormality in the chest, and the abdomen was flat and soft.

[Blood examination at the first visit to our hospital] Table 1 summarizes the hematological and biochemical findings at the initial

Table 1. Hematological and biochemical findings at initial examination

WBC	5820 /μl	TP	7.2 g/dl	LDH	174 U/l	Na	139 mmol/l	CEA	4.1 ng/ml
RBC	442×10^4 /μl	Alb	3.9 g/dl ↓	BUN	26 mg/dl ↑	K	4.9 mmol/l	CA19-9	26.5 ng/ml
Hb	12.8 g/dl ↓	AST	20 U/l	Crn	1.28 mg/dl ↑	Cl	102 mmol/l	SCC	1.6 ng/ml ↑
Ht	40.80 %	ALT	7 U/l	T.Cho	223 mg/dl	Ca	9.6 mg/dl	*H. pylori*-IgG	30 U/l ↑
Plt	37.7×10^4 /μl	γ-GTP	24 U/l	UA	7.9 mg/dl ↑				

Arrows pointing up or down indicate a reduction or elevation of the parameter level, respectively. Alb, albumin; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CA19-9, carbohydrateantigen 19-9; CEA, carcinoembryonic antigen; Crn, creatinine; γ-GTP, gamma-glutamyl transpeptidase; IgG, immunoglobulin G; Hb, hemoglobin; Ht, hematocrit; LDH, lactate dehydrogenase; Plt, platelets; RBC, red blood cell; SCC, squamous cell carcinoma antigen; T. Cho, total cholesterol; TP, total protein; UA, urinalysis; WBC, white blood cell



a

b c

Fig. 1. Endoscopic images of esophageal cancer
The images reveal a IIc lesion in the mid-esophagus.
a: LCI, b: BLI, c: WLI

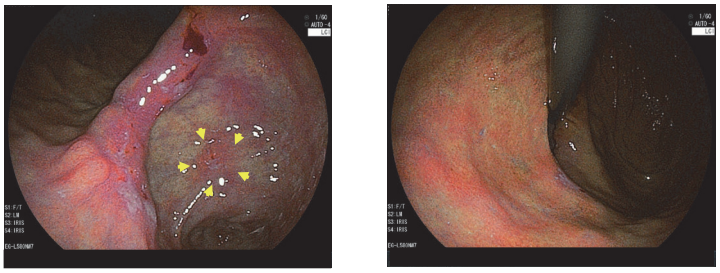
examination. These results revealed mild anemia, hypoalbuminemia, and a decreased renal function. One tumor marker (the SCC antigen) was mildly elevated and the serum anti-*Helicobacter pylori* (*H. pylori*) antibody result was positive (titer 30 U/ml).

[Upper gastrointestinal endoscopy] Prior LCI revealed a reddish, irregular, shallow depressed lesion (10 mm in diameter; IIc) in the mid-esophagus (Fig. 1a), which was displayed as a brownish area upon BLI (Fig. 1b) and was clearly demarcated from the non-tumor area upon WLI (Fig. 1c). SCC was detected in the same area, and the depressed surface was not markedly uneven, suggesting that the lesion was intramucosal. In addition, a highly deformed and irregular depressed lesion with fold convergence was discovered in the incisura of the lesser curvature (Fig. 2a). LCI also revealed a small IIc lesion in the lesser curvature of the antrum (Fig. 2a, yellow arrows). Biopsies of the two lesions revealed that they were well-differentiated adenocarcinomas. The background gastric mucosa exhibited corporal atrophy with diffuse redness, suggestive of *H. pylori*-associated gastritis (Fig. 2b).

[Colonoscopy] Colonoscopy revealed a well-defined, rounded, ulcerative tumor (type 2) in

the transverse colon (Fig. 3a), and a biopsy specimen revealed that it was a well-differentiated adenocarcinoma. In addition, multiple colorectal polyps were discovered at the same time (Fig. 3b).

[NBI magnified endoscopy and ESD for esophageal cancer] NBI magnified endoscopy was performed on the esophageal lesion, and its microvasculature was classified as type B1 according to the Esophageal Association classification[12] (Fig. 4a). ESD was performed on the esophageal lesion based on magnification endoscopic findings. Pathologically, the lesion was



a b

Fig. 2. Endoscopic images of two gastric cancer lesions
LCI reveals IIc lesions in the incisura of the lesser curvatute (a), and in the lesser curvature of the antrum (a, yellow arrows). The corporal gastric mucosa exhibited atrophy with diffuse redness (b).

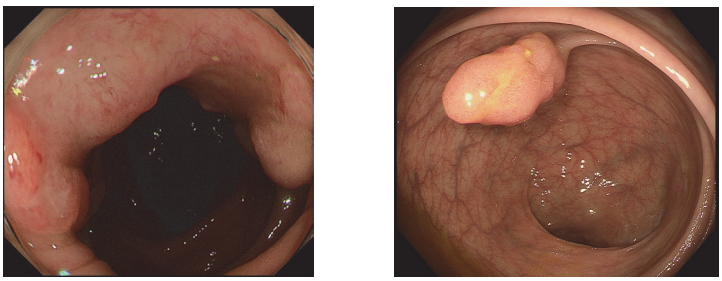


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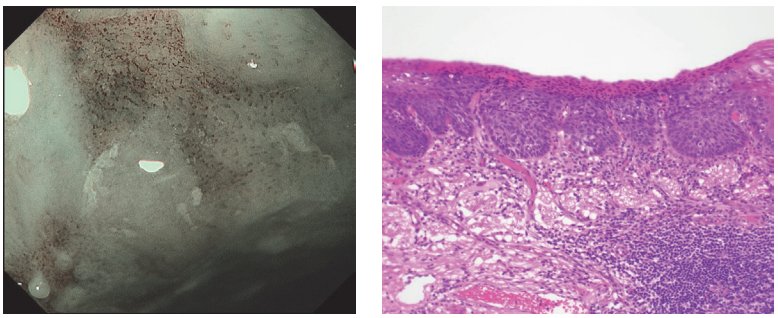
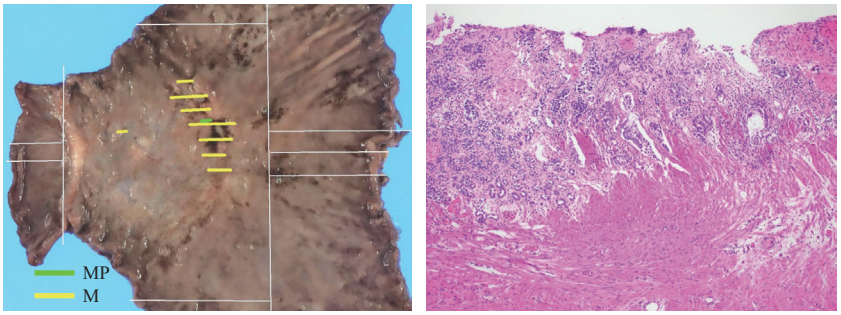
Fig. 3. Endoscopic images of colon cancer and rectal polyp
Colonoscopy reveals a type 2 tumor in the transverse colon (a), and a rectal polyp (b).



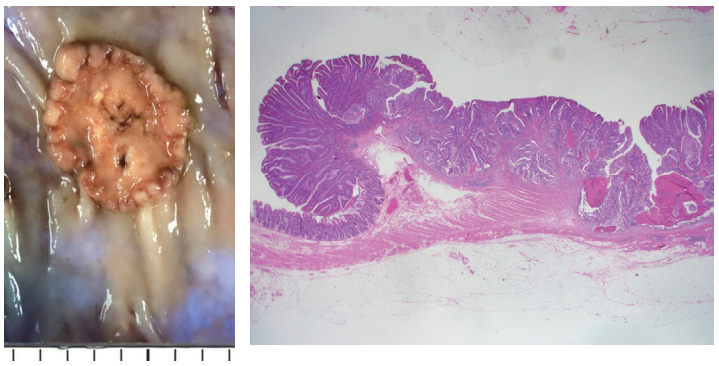
a b

Fig. 4. NBI magnified endoscopy and a histological specimen for esophageal cancer
The microvasculature of the esophageal lesion was classified as type B1 (a). Pathologically, the tumor cells were limited to the mucosa (b) (hematoxylin-eosin stain, 20 × 10 magnification).



a b

Fig. 5. The fixed and histological specimens of the resected gastric cancer
The fixed specimen reveals the two cancers in the incisura and antrum (a). Pathologically, the main lesions were located in the mucosa, with some invasion into the muscle layer (b) (hematoxylin-eosin stain, 10 × 4 magnification).



a b

Fig. 6. The fixed and histological specimens of the resected transverse colon cancer
The fixed specimen reveals a type 2 tumor (a). The cancer lesion invaded the muscle layer (b) (hematoxylin-eosin stain, 10 × 1.2 magnification).

7 × 5 mm in size and classified as 0-IIc, and the tumor cells were limited to the mucosa (SCC, pT1a-LPM, INFa, ly0, v0, pHM0 [3 mm], pVM0, pR0, pCurA) (Fig. 4b).

[Simultaneous surgical operation for multiple gastric cancers and colorectal cancer]

The preoperative clinical diagnoses of the two gastric cancers were (1) ML, Less, type 0-IIc, cT1bN0M0, and cStage IA, and (2) L, Less, type 0-IIc, cT1aN0M0, cStage IA; that of the colon cancer was type 2, cT2N0M0, cStage I. Thus, the patient was treated with surgery. Laparoscopy-assisted distal gastrectomy with D1+ lymph-node dissection (Fig. 5a) and transverse colectomy with D2 lymph-node dissection (Fig. 6a) were performed for the gastric and colorectal lesions, respectively. The reconstruction methods were residual gastroduodenal anastomosis (Billroth I method) and colonic distal anastomosis, respectively. The main lesion in the stomach was a tumor arising from an ulcer scar, and was predominantly intramucosal with partial infiltration into the muscularis propria (MP) (Fig.5 a, b). In addition, the secondary lesion in the lesser curvature of the antrum was limited to the mucosa (M). The final pathological results for the main lesion were as follows: M; Less-Ant; size, 30 × 15 mm; 0-IIc; tub 1 > tub 2; pT2 (MP); UL1; Ly0; V0 (Victoria blue-hematoxylin

and eosin staining [VB-HE]); PM0 (8 cm); DM0 (4 cm); pN0 (0/17); and pStage ⅠB. Those for the secondary lesion were as follows: L; Less; size, 5 × 5 mm; 0-IIc; tub 1; pT1a (M); UL0; Ly0; V0 (VB-HE); and pStage ⅠA. The resected specimen of the transverse colon revealed a rounded, raised lesion of approximately 30 mm in diameter, and the cancer had invaded the MP (Fig.6). The final pathological results were as follows: size, 32 × 27 mm; 2 (2/5 circ); tub 1 > tub 2; pT2 (MP); int; intermediate type (INFb); BD; grade 1; Ly0; V1a (VB-HE); Pn0; PM0 (40.5 cm); DM0 (10.5 cm); RM0; pN0 (0/8); and pStage Ⅰ. This tumor was negative for RAS and BRAF p.V600E mutations.

DISCUSSION

We reported a case of synchronous MPMTs of the esophagus, stomach, and colon, detected by means of endoscopic screening. The esophageal cancer in most reports of triple cancer is advanced, requiring surgery. As esophageal cancer has a poor prognosis, its early detection is highly beneficial, as endoscopic treatment is still possible. The patient had a history of copious alcohol consumption and exhibited alcohol flushing syndrome; he also had a history of smoking and a family history of cancer. In patients with multiple cancer risk factors, it is important to consider the possibility of MPMTs.

Among the reported cases of triple cancer (esophageal, gastric, and colorectal cancers) in Japan, cases in which endoscopic treatment was performed for esophageal cancer are listed in Table 2. We searched the Igaku Chuo Zasshi (Japanese) database for records from 1995 to 2021. Including our case, six cases were selected[13−17]. The patient ages ranged from 55 to 74 years (mean age, 64 years); all six were men, and four of them had three early-stage cancers (cases 1, 2, 4, and 5). All patients are alive and have experienced no recurrence to date. Tumors were detected via screening or surveillance in 4 of 6 cases.

H. pylori infection is a major risk factor for gastric cancer[18]. In this case, in addition to *H. pylori* infection, the patient's father had a history of gastric cancer. Factors that can lead to the development of multiple cancers include aging, alcohol consumption, smoking, and genetic factors. Heterozygous mutations in the *aldehyde dehydrogenase-2* (*ALDH2*) gene increases the risk of esophageal cancer[19, 20]. Lynch syndrome (hereditary non-polyposis colorectal cancer) increases the risk of developing colorectal, endometrial, ovarian, stomach, small intestine, hepatobiliary, renal pelvic, and ureteral cancer[21]. This case, however, did not meet the Amsterdam criteria[22] or criteria of the revised Bethesda guidelines[23].

In this case, the simultaneous use of LCI and BLI may have contributed to the early detection of esophageal cancer. Fujifilm Corporation (Tokyo, Japan) has developed novel laser imaging systems

Table 2. Triple cancer of the esophagus, stomach, and colon - cases of endoscopic treatment for esophageal cancer

Case	First author	Publish year	Age	Gender	Synchronous/ metachronous	Esophageal cancer			Gastric cancer			Colon cancer			Observation periods	Prognosis	Method of discovery
						Macroscopic type	Depth	Treatment	Macroscopic type	Depth	Treatment	Macroscopic type	Depth	Treatment			
1	Bando	1997	74	Male	Synchronous	0-IIb	EP	EMR	0-IIa	M	EMR	0-IIb	M	Surgery	8 mo	Alive	Anemia
2	Murai	1998	64	Male	Synchronous	0-IIb	M	EMR	0-IIa	M	EMR	0-IIa+IIc	M	Surgery	24 mo	Alive	Surveillance
3	Nonaka	2001	55	Male	Metachronous	0-IIc	SM	ESD	0-IIc	M	Surgery	2	SS	Surgery	9 mo	Alive	Abdominal pain
4	Saeki	2006	60	Male	Synchronous	0-IIb	LPM	EMR	0-IIc, 0-IIc+IIa	SM, M	Surgery	0-IIa+IIc	M	EMR	31 mo	Alive	Stool occult
5	Miyazaki	2009	64	Male	Synchronous	0-IIc	LPM	ESD	0-IIc+IIa	SM	Surgery	0-IIa+IIc	SM	Surgery	33 mo	Alive	Endoscopic screening
6	Our case	2022	67	Male	Synchronous	0-IIc	LPM	ESD	0-IIc	MP	Surgery	2	MP	Surgery	15 mo	Alive	Endoscopic screening

EMR, endoscopic mucosal resection; EP, epithelial; ESD, endoscopic submucosal dissection; LPM, lamina propria mucosa; M, mucosal; MP, muscularis propria; SM, submucosal

and multi-light technologies. A laser endoscopic system (LASEREO) with BLI was made available in Japan in 2011, and a system with LCI in 2014. In SCCs of the esophagus, BLI yields a high color contrast between lesions (displayed in brown) with intrapapillary capillary loops and the surrounding area, and it is useful in the early detection of esophageal cancers, visualized as brownish areas with vessels forming dot-like shapes, without magnification.

LCI provides sufficient light intensity, yielding bright images even in distant views, by using novel processing technology. LCI contributes to the improved diagnosis of various gastrointestinal tract lesions that are difficult to diagnose with WLI alone. Nakamura *et al*.[8] investigated the usefulness of LCI in detecting superficial esophageal SCCs compared with BLI-bright and WLI. They revealed that LCI improved the visibility of tumors compared with WLI, almost to the same extent as BLI-bright. In addition, Ono *et al*.[11] discovered that LCI followed by WLI examination was more effective than WLI followed by LCI examination in detecting neoplastic lesions in the pharynx, esophagus, and stomach.

CONCLUSIONS

We reported a case of synchronous triple cancer of the esophagus, stomach, and colon, detected by means of gastrointestinal screening endoscopy. In patients with multiple cancer risk factors, it is important to consider the possibility of MPMTs, and upper gastrointestinal observation combined with IEE is useful in the early detection of lesions.

CONFLICTS OF INTEREST

The authors declare no conflict of interest associated with this manuscript.

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