Figure S4 Schema of crosstalk between Hh and EMT signal pathways in esophageal cancers. The primary transcriptional factor GLI1 and an EMT regulator TWIST1 regulate another EMT regulator ZEB2, which activates any gene including membrane type receptors (*PDGFRA*, *EDNRA*, *CXCR4*, *VEGFR2*, and *TRKB*) [9].
(TIF)

Figure S5 Expression levels of *HIF1A*, *HIF1B*, *HIF2A*, and *LOXL2* in two sets of biopsy and surgical samples (different and identical cases). Over-expression of *HIF1A* and its target *LOXL2* is observed only in surgically resected esophageal tumors (different cases).
(TIF)

Figure S6 Expression levels of *NFKB1* and *TGFBR2* in two sets of biopsy and surgically resected tumor samples (different and identical cases) and in biopsy and surgically resected non-cancerous tissues (normal). Over-expression of *NFKB1* and *TGFBR2* is observed in all the sets of surgically resected samples. $*P<0.05$.
(TIF)

Table S1 219 up-regulated genes in 66 surgically resected esophageal tumors.
(DOC)

Table S2 716 up-regulated genes in 18 surgically resected esophageal tumors.
(DOC)

Table S3 Clinicopathological information of biopsy samples from different cases with esophageal squamous cell carcinoma.
(DOC)

Table S4 Clinicopathological information of surgical samples from different cases with esophageal squamous cell carcinoma.
(DOC)

Table S5 Clinicopathological information of biopsy and surgical samples from different cases with esophageal squamous cell carcinoma.
(DOC)

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Author Contributions

Conceived and designed the experiments: KA KM MM A. Ohtsu TY HS. Performed the experiments: KA TN AA. Analyzed the data: KA HS. Contributed reagents/materials/analysis tools: KM HI YT A. Ochiai NH HD MM A. Ohtsu. Wrote the paper: KA HS.

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The Laryngoscope

Diagnosis of the Extent of Advanced Oropharyngeal and Hypopharyngeal Cancers by Narrow Band Imaging With Magnifying Endoscopy

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Objectives/Hypothesis: Narrow band imaging combined with magnifying endoscopy (NBI-ME) is useful for the detection of superficial cancer in the oropharynx, hypopharynx, and esophagus. We used NBI-ME to evaluate the frequency of superficial cancer spread (SCS) contiguous with advanced oropharyngeal and hypopharyngeal cancers and esophageal cancers.

Study Design: Retrospective.

Methods: We retrospectively studied 45 patients with oropharyngeal and hypopharyngeal cancer and 44 with esophageal cancer who underwent NBI-ME from October 2006 through April 2009. The following variables were evaluated: 1) the frequency of SCS contiguous with advanced oropharyngeal and hypopharyngeal cancer and esophageal cancer, and 2) the influence of SCS contiguous with advanced oropharyngeal and hypopharyngeal cancer on clinical T category and clinical stage.

Results: SCS contiguous with the primary tumor was found in 49% (22/45) of the patients with advanced oropharyngeal and hypopharyngeal cancer and in 52% (23/44) of those with advanced esophageal cancer. When SCS contiguous with the primary tumor was included in the evaluation of tumor size in advanced oropharyngeal and hypopharyngeal cancer, the clinical T category and clinical stage were revised in 20% (9/45) and 4% (2/45) of patients, respectively; SCS was $\leq$2 cm in 64% of cases (14/22) and between >2 cm and $\leq$4 cm in 36% (8/22).

Conclusions: NBI-ME should be included in the pretreatment diagnostic work-up to evaluate lesion extent and decide optimal surgical margins and radiation fields in patients with advanced oropharyngeal and hypopharyngeal cancer.

Key Words: Narrow band imaging, magnifying endoscopy, lesion extent, head and neck cancer.

Level of Evidence: 3b

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INTRODUCTION

The advent of narrow band imaging (NBI) and high-resolution magnifying endoscopy (ME) has facilitated the detection of superficial cancer in the oropharynx, hypopharynx, and esophagus.[1–6] These techniques have also enabled the lateral spread of superficial cancer contiguous with advanced oropharyngeal, hypopharyngeal, and esophageal tumors to be visualized, allowing an accurate evaluation of lesion extent, which is essential for setting surgical margins and radiation fields. We used NBI combined with ME (NBI-ME) to examine the frequency of superficial cancer spread (SCS) contiguous with advanced oropharyngeal and hypopharyngeal cancers and esophageal cancers.

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MATERIALS AND METHODS

We retrospectively studied 45 patients with oropharyngeal and hypopharyngeal cancer and 44 with esophageal cancer who underwent NBI-ME at Kitasato University Hospital from October 2006 through April 2009. All patients met all of the following criteria: 1) no previous treatment for head and neck cancer or esophageal cancer, 2) a histopathological diagnosis of squamous-cell carcinoma, 3) advanced cancer, 4) computed tomography (CT) had been performed, and 5) chromoendoscopy with Lugol's iodine solution had been performed (only for patients with advanced esophageal cancer).

The following variables were evaluated: 1) the frequency of SCS contiguous with advanced oropharyngeal and hypopharyngeal cancer and esophageal cancer, and 2) the influence of SCS contiguous with advanced oropharyngeal and hypopharyngeal cancer on clinical T category and clinical stage. In this study, we performed NBI with a high-definition videoendoscopy system (with a CV-260SL processor and a CLV-260SL light source; Olympus Optical Co., Ltd., Tokyo, Japan) and an optical magnifying endoscope with a system that could magnify objects up to 80 times (GIF type H260Z videoendoscope; Olympus). A 1.5% solution of Lugol dye was used to perform chromoendoscopy according to the Lugol dye-staining method (Lugol

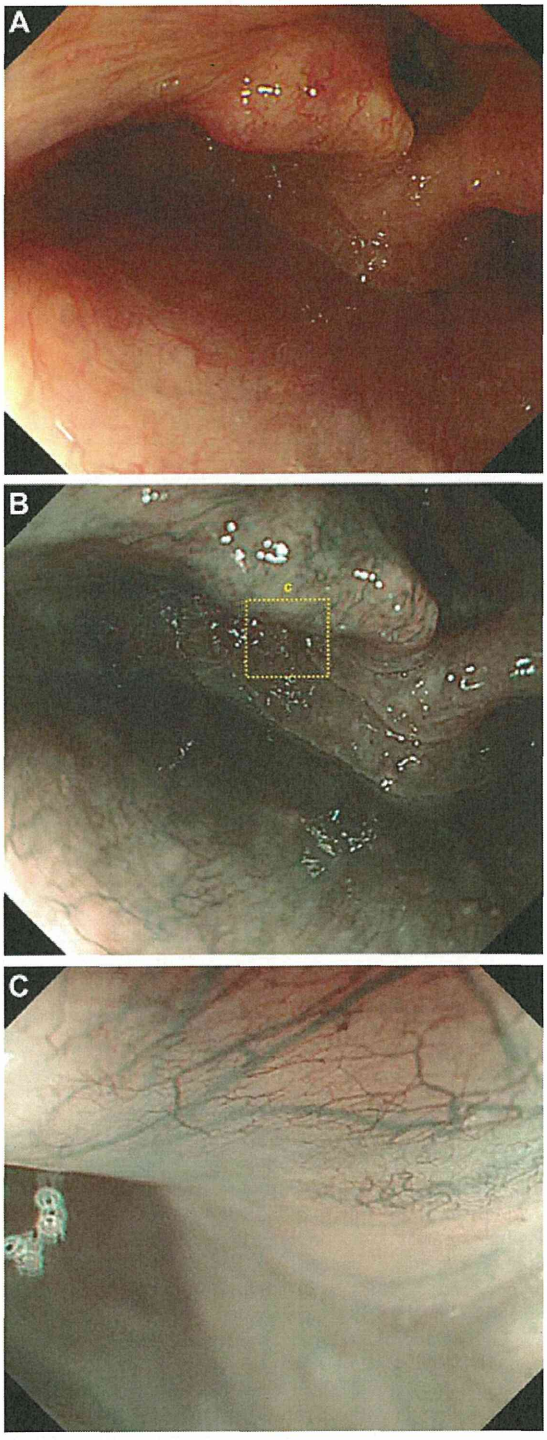

Fig. 1. Normal mucosa in the left postcricoid area. (A) White light endoscopy. (B) Narrow band imaging. (C) Narrow band imaging-magnifying endoscopy, showing a regular microvascular pattern beneath the epithelium.

chromoendoscopy)[7] in all patients with esophageal cancer. Examinations in patients with advanced oropharyngeal and hypopharyngeal cancer were performed in the following order: white light endoscopy, NBI endoscopy, and NBI-ME. In patients with advanced esophageal cancer, examinations were done in the following order: white light endoscopy, NBI endoscopy, NBI-ME, and Lugol chromoendoscopy. Superficial cancer was defined as a lesion with high-grade intraepithelial neoplasia or microinvasive cancer as diagnosed endoscopically according to the World Health Organization classification of tumors.[8] Advanced cancer was defined as a lesion with deeper invasion. Superficial cancer contiguous with the primary tumor was diagnosed endoscopically on the basis of 1) a well-demarcated area and 2) an irregular microvascular pattern.[2–6] Endoscopic images were reviewed by an otolaryngological endoscopist (h.m.) and a gastrointestinal endoscopist (c.k.). Clinical T category and clinical stage were assessed according to the 7th edition of the International Union Against Cancer (UICC) tumor-node-metastasis (TNM) staging system.[9] At the time of endoscopy, we estimated the size of the lesion by placing biopsy forceps (FB-25K-1; Olympus) alongside the lesion; the fully opened cup of the forceps was 6 mm in diameter.

Normal mucosa in the left postcricoid area is shown in Figure 1. On white light endoscopy (Fig. 1A) and NBI (Fig. 1B), a regular microvascular pattern beneath the epithelium was difficult to identify. However, NBI-ME (Fig. 1C) clearly showed a regular microvascular pattern beneath the epithelium. Advanced hypopharyngeal cancers arising in the left postcricoid area are shown in Figure 2 and Figure 3.

In the first case, the tumor was nonulcerative and was situated mainly in the submucosa. SCS extended from the surface of the lesion to its distal border. The greatest tumor dimension was 15 mm in the transverse plane (Fig. 2A) and 22 mm in the coronal plane (Fig. 2B) on CT, and about 25 mm on white light endoscopy (Fig. 2C). Therefore, the lesion was classified as a clinical T2 tumor. NBI showed a well-demarcated, brownish area on the surface of the lesion (Fig. 2D). NBI-ME revealed an irregular microvascular pattern (Fig. 2E). SCS about 10 mm in diameter was contiguous with the anal side of the primary tumor (Fig. 2F), but there was no upgrade of the clinical T category.

In the next case, the tumor was ulcerative and accompanied by SCS only at the border of the lesion. The greatest tumor dimension was 11 mm in the transverse plane (Fig. 3A) and 24 mm in the coronal plane (Fig. 3B) on CT, and about 25 mm on white light endoscopy (Fig. 3C). The lesion was classified as a clinical T2 tumor. NBI showed a well-demarcated, brownish area in the lateral wall (Fig. 3D). NBI-ME revealed an irregular microvascular pattern. SCS extended for about 30 mm from the postcricoid area to the lateral wall via the pyriform sinus and was contiguous with the primary tumor (Fig. 3E). When this spread was included in the evaluation, the clinical T category was upgraded from T2 to T3.

A case of advanced esophageal cancer is shown in Figure 4. White light endoscopy revealed advanced esophageal cancer, occupying half of the circumference of the esophagus (Fig. 4A). NBI showed a well-demarcated, brownish area at the border of the primary tumor (Fig. 4B). NBI-ME revealed an irregular microvascular pattern (Fig. 4C). SCS as an unstained area at the border of the primary tumor was seen on Lugol chromoendoscopy (Fig. 4D). Because the clinical T category of esophageal cancer is based on the depth of tumor invasion, the presence of SCS contiguous to the primary tumor does not alter the classification of clinical T category.

RESULTS

Table I shows the demographic characteristics of the patients. The study group comprised 78 men (88%) and 11 women (12%), with a mean age (±standard

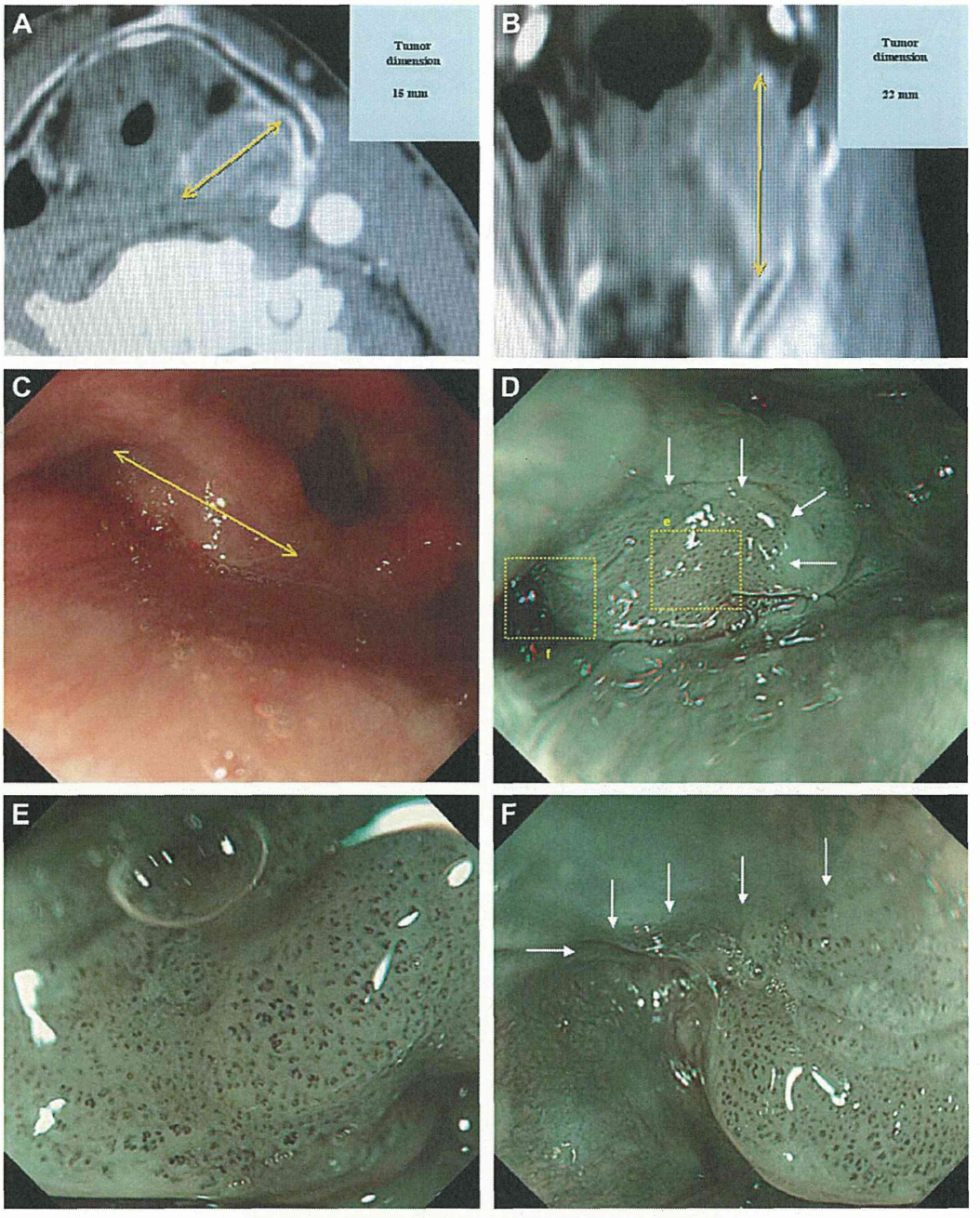

Fig. 2. Advanced hypopharyngeal cancer arising in the left postcricoid area. The tumor was nonulcerative and situated mainly in the submucosa. Superficial cancer spread extended from the surface of the lesion to its distal border. (A) The greatest tumor dimension was 15 mm in the transverse plane on computed tomography (CT). (B) The greatest tumor dimension was 22 mm in the coronal plane on CT. (C) The greatest tumor dimension was about 25 mm on white light endoscopy. (D) Narrow band imaging showed a well-demarcated, brownish area (arrows). (E) Narrow band imaging-magnifying endoscopy revealed an irregular microvascular pattern. (F) Superficial cancer spread about 10 mm in diameter was contiguous with the anal side of the primary tumor (arrows).

deviation) of 66 ± 8.7 years. Among six patients (7%) with oropharyngeal cancer, the primary tumor was located in the anterior wall in four patients (5%), the lateral wall in one patient (1%), and the posterior wall in one patient (1%). Among 39 patients (44%) with hypopharyngeal cancer, the primary tumor was located in the pyriform sinus in 22 patients (25%), the postcricoid area in nine patients (10%), and the posterior wall in eight patients (9%). A total of 44 patients (49%) had primary esophageal cancer.

SCS contiguous with the primary tumor was found in 49% (22/45) of the patients with advanced oropharyngeal and hypopharyngeal cancer and in 52% (23/44) of those with advanced esophageal cancer. In patients with

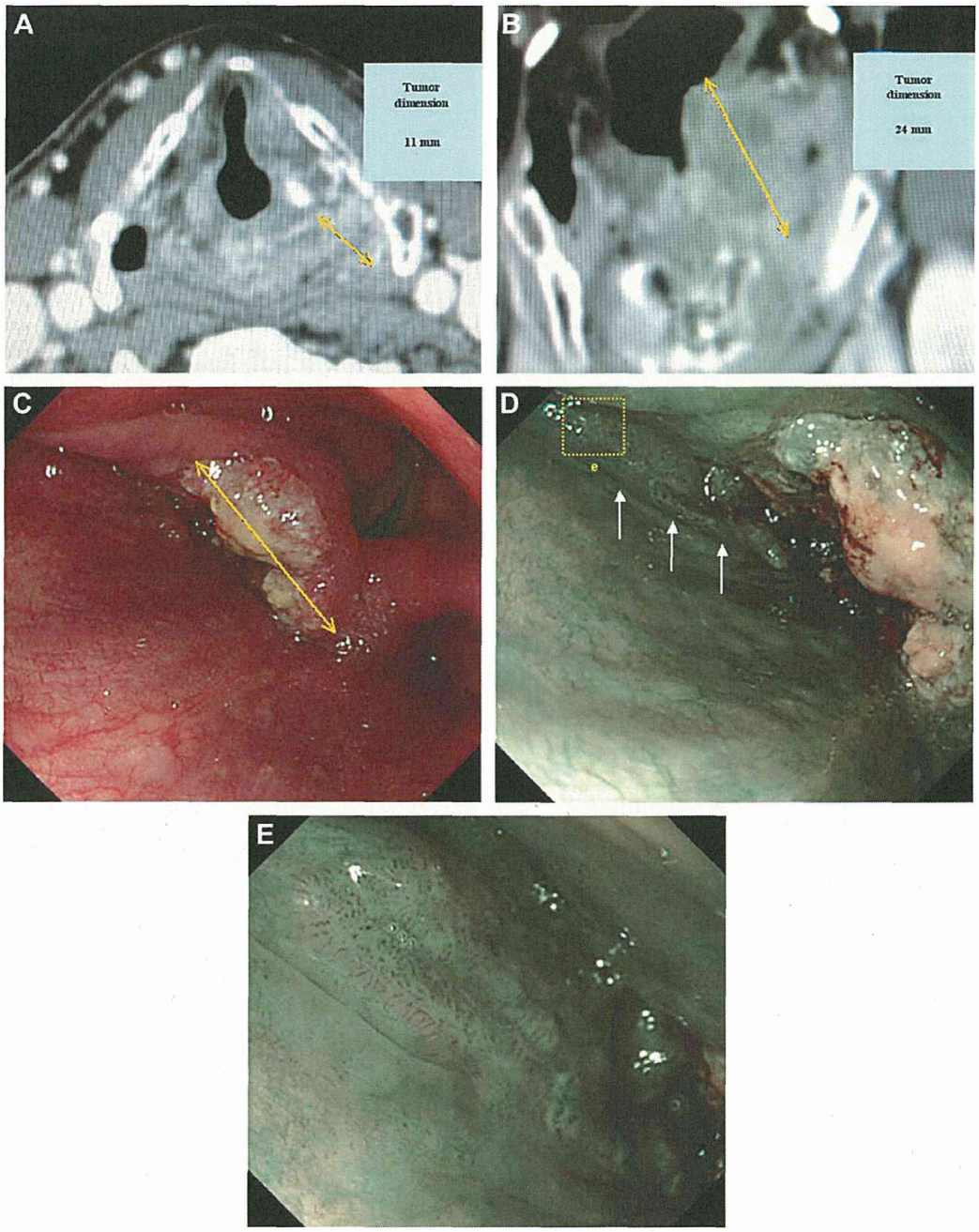

Fig. 3. Advanced hypopharyngeal cancer arising in the left postcricoid area. The tumor was ulcerative, and superficial cancer spread was present only at its border. (A) The greatest tumor dimension was 11 mm in the transverse plane on computed tomography (CT). (B) The greatest tumor dimension was 24 mm in the coronal plane on CT. (C) The greatest tumor dimension was about 25 mm on white light endoscopy. (D) Narrow band imaging showed a well-demarcated, brownish area (arrows). (E) Narrow band imaging-magnifying endoscopy revealed an irregular microvascular pattern. Superficial cancer spread extended for about 30 mm from the postcricoid area to the lateral wall via the pyriform sinus and was contiguous with the primary tumor.

advanced esophageal cancer, the ability to detect SCS was similar for Lugol chromoendoscopy and NBI-ME. The clinical T category was revised in nine patients (20%) who had advanced oropharyngeal and hypopharyngeal cancer; it was upgraded from T1 to T2 in two patients (4%) and from T2 to T3 in seven patients (16%). The clinical stage was revised in two patients (4%); one patient (2%) was upgraded from stage I to II, and one patient (2%) was upgraded from stage II to III. In patients with advanced esophageal cancer, there was no change in clinical T category or in clinical stage (Table II).

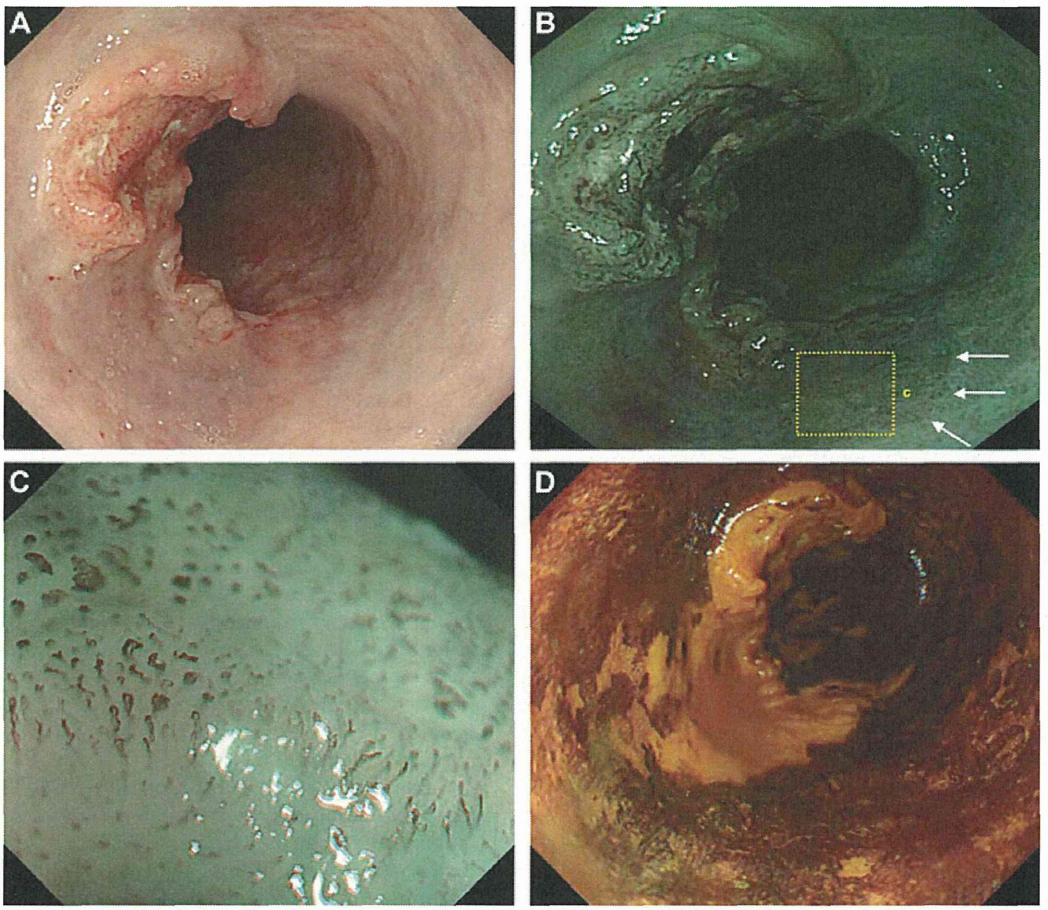

Fig. 4. Advanced esophageal cancer. (A) White light endoscopy revealed advanced esophageal cancer. (B) Narrow band imaging showed a well-demarcated, brownish area at the border of the primary tumor (arrows). (C) Narrow band imaging-magnifying endoscopy revealed an irregular microvascular pattern. (D) Superficial cancer spread appeared as an unstained area at the border of the primary tumor on Lugol chromoendoscopy.

TABLE I.
Patient and Lesion Demographics (n = 89).

Gender, no. (%)	
Male	78 (88)
Female	11 (12)
Age, mean ± SD, yr	66 ± 8.7
Range, yr	45–89
Site of primary cancer, no. (%)	
Oropharynx	6 (7)
Anterior wall	4 (5)
Lateral wall	1 (1)
Posterior wall	1 (1)
Hypopharynx	39 (44)
Pyriform sinus	22 (25)
Postcricoid area	9 (10)
Posterior wall	8 (9)
Esophagus	44 (49)

SD = standard deviation.

The dimensions of SCS contiguous with the primary tumor are summarized in Table III. In advanced oropharyngeal and hypopharyngeal cancer, SCS was ≤2 cm in 64% of cases (14/22), between >2 cm and ≤4 cm in 36% (8/22), and >4 cm in 0% (0/22). In advanced esophageal cancer, SCS was ≤2 cm in 52% (12/23) of cases, between >2 cm and ≤4 cm in 30% (7/23), and >4 cm in 17% (4/23). The size of SCS did not differ between patients with advanced oropharyngeal and hypopharyngeal cancer and those with advanced esophageal cancer (P =.237).

DISCUSSION

A nationwide survey conducted by the Japan Society for Head and Neck Cancer in 2005 reported that no patient with oropharyngeal and hypopharyngeal cancer had carcinoma in situ at initial presentation, suggesting that is it very difficult to visually confirm superficial cancer in the oropharynx and hypopharynx.[10] Laryngoscopy was conventionally used to detect oropharyngeal and hypopharyngeal cancer. However, the advent of NBI-ME has markedly improved the ability to visualize superficial cancer,[2–6] facilitating the diagnosis of SCS

contiguous with advanced cancer. In the present study of SCS contiguous with advanced oropharyngeal cancer and hypopharyngeal cancer, the rates of clearly visualizing "well-demarcated areas" and "irregular microvascular patterns," considered endoscopic characteristics of superficial cancer, on white light endoscopy, NBI, and NBI-ME were 23% (5/22), 82% (18/22), and 100% (22/22) for the former, respectively; and 14% (3/22), 77% (17/22), and 100% (22/22) for the latter, respectively. Therefore, well-demarcated areas and irregular microvascular patterns of SCS were better visualized by NBI and NBI-ME than by white light endoscopy. Furthermore, NBI-ME allowed definitive visualization of both of these characteristics. Muto et al. reported that the sensitivities and accuracies for the diagnosis of superficial cancer in the oropharynx and hypopharynx were 7.7% and 62.9% for white light endoscopy, respectively, as compared with 100% and 86.7% for NBI-ME, respectively. For the diagnosis of superficial esophageal cancer, the sensitivities and accuracies were 55.2% and 56.5% for white light endoscopy, respectively, and 97.2% and 88.9% for NBI-ME, respectively.[5] In the present study, a histopathological diagnosis could be made in 29 (64%) of 45 cases of SCS that were diagnosed endoscopically (14 cases of oropharyngeal cancer and hypopharyngeal cancer and 15 cases of esophageal cancer). However, superficial cancer was histologically confirmed in all cases. These findings indicate that the diagnostic accuracy of NBI-ME for SCS is extremely high.

Lugol chromoendoscopy has been used to diagnose lesion extent in patients with esophageal cancer,[7] but cannot be used to examine the oropharynx and hypopharynx because of the high risk of aspiration and the strong local irritation caused by iodine. In our study, all cases of SCS contiguous with advanced esophageal cancer detected on Lugol chromoendoscopy were also visualized on NBI. This finding suggested that NBI is also likely to be useful for the confirmation of SCS contiguous with advanced oropharyngeal and hypopharyngeal cancer, which cannot be evaluated on Lugol chromoendoscopy. In our study, SCS was associated with 49% of advanced oropharyngeal and hypopharyngeal cancers and 52% of advanced esophageal cancers (i.e., about one half of the patients with each type of cancer). To our knowledge, this is the first time similar frequencies of SCS contiguous with the primary tumor in patients with advanced oropharyngeal and hypopharyngeal cancer, and those with advanced esophageal cancer were reported. Therefore, we believe that our results are very important. Moreover, in 18% (8/45) of patients with advanced oropharyngeal and hypopharyngeal cancer, SCS contiguous with the primary tumor exceeded 2 cm. We therefore consider NBI-ME to be essential for the determination of appropriate surgical margins and radiation fields.

TABLE II.
Frequency of Superficial Cancer Spread Contiguous With Primary Tumor and Effects on Clinical T Category and Clinical Stage.

	Advanced Oropharyngeal/ Hypopharyngeal Cancer (n = 45)	Advanced Esophageal Cancer (n = 44)
Frequency of superficial cancer spread, no. (%)		
NBI-ME	22 (49)	23 (52)
Lugol chromoendoscopy	NE	23 (52)
Frequency of changes in clinical T category, no. (%)	9 (20)	0 (0)
From clinical T1 to T2	2 (4)	
From clinical T2 to T3	7 (16)	
Frequency of changes in clinical stage, no. (%)	2 (4)	0 (0)
From clinical stage I to II	1 (2)	
From clinical stage II to III	1 (2)	

NBI = narrow band imaging; ME = magnifying endoscopy; NE = not evaluated.

TABLE III.
Dimensions of Superficial Cancer Spread.

	Advanced Oropharyngeal/ Hypopharyngeal Cancer (n = 22)	Advanced Esophageal Cancer (n = 23)	*P* Value*
0 cm to ≤2 cm	14 (64%)	12 (52%)	
>2 cm to ≤4 cm	8 (36%)	7 (30%)	
>4 cm	0 (0%)	4 (17%)	.237

*Calculated using Mann-Whitney *U* test.

Because the 7th edition of the UICC TNM staging system does not include contiguous SCS as a staging factor,[9] we examined whether clinical T category and clinical stage were altered by including contiguous SCS in the greatest dimension of the primary tumor. In esophageal cancer, the clinical T category is determined by the depth of primary tumor invasion.[9] Consequently, the presence of SCS contiguous with the primary tumor does not change the clinical T category. In contrast, the clinical T category of oropharyngeal and hypopharyngeal cancer depends on the greatest dimension of the primary tumor.[9] The inclusion of SCS contiguous with the primary tumor in the evaluation of tumor size may thus alter the clinical T category, potentially affecting the clinical stage grouping. When we included SCS contiguous with the primary tumor in the calculation of the greatest tumor dimension in patients with oropharyngeal and hypopharyngeal cancer, the clinical T category was upgraded in 20% of cases. However, the effect on clinical stage was minimal. Clinical T categories were decided before it was possible to clinically evaluate SCS contiguous with the primary tumor. With improved diagnostic techniques, contiguous SCS can now be evaluated. Therefore, a discussion of whether to include contiguous SCS in the evaluation of clinical T category now appears to be warranted.

CONCLUSION

In this study, advanced oropharyngeal and hypopharyngeal cancer is frequently associated with contiguous SCS. NBI-ME should be included in the pretreatment diagnostic work-up to evaluate lesion extent

and decide optimal surgical margins and radiation fields.

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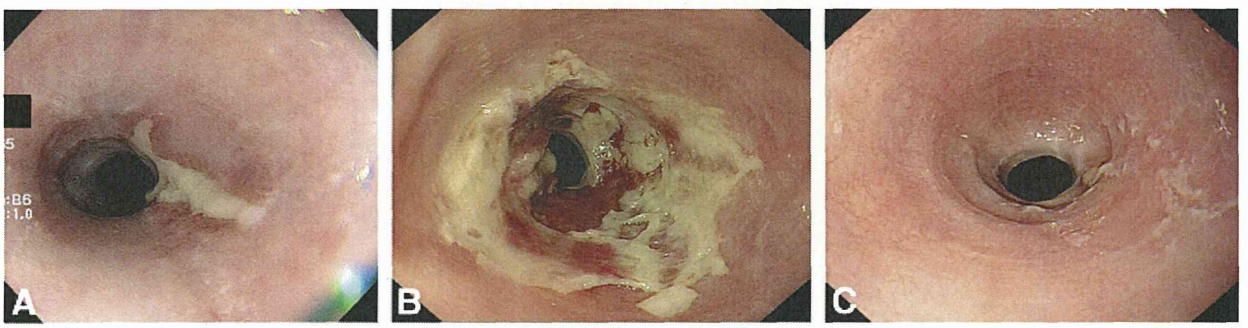
Commentary

Although rare, fibrovascular polyps of the esophagus (FVPEs) comprise most of this organ's benign intraluminal tumor-like lesions. FVPE are composed of fibrous tissue, adipose tissue, and vascular structures and are covered by normal squamous epithelium. Depending on which histologic components predominate, FVPEs also may be referred to as lipomas, fibromas, fibrolipomas, fibromyxomas, and fibroepithelial polyps. With an average length of 15 cm, FVPEs arise from just below the cricopharyngeus muscle in the area known as Killian's or Laimer's triangle. When small, these lesions are asymptomatic. Symptoms only develop when FVPEs reach a large size and include dysphagia, regurgitation of the polyp into the mouth, bleeding, dyspnea, stridor, wheezing, choking, and even asphyxiation. One reported case described a patient who regurgitated a giant FVPE into his mouth and captured it between his teeth until it could be removed endoscopically. Upper GI series and endoscopy can be diagnostic, but an FVPE may be missed at endoscopy because the polyp is covered by normal mucosa and can be highly mobile. Surgical excision or endoscopic resection is definitive treatment, but care must be taken to ensure that the prominent vessels in the stalk are completely ligated or coagulated. The stalk should be completely excised or recurrence is possible. I think of the folk album Arkansas Traveler, on which Michelle Shocked popularized the now classic tune "Come a Long Way" singing "I come a long way, I come a long way and never even left LA." Well these polyps also come a long way, but never leave the area of the cricopharyngeus. If regurgitated out from their point of residence, like Michelle, they leave the patient—and the physician—shocked.

Lawrence J. Brandt, MD,
Associate Editor for Focal Points

A case of esophageal ulcer caused by alendronate sodium tablets



A 75 year old woman was referred to our hospital with dysphagia. Esophagoscopic examination revealed a shallow ulceration at the upper esophageal region (**A**). She had no history of esophageal disorder.

The ulceration gradually improved without treatment, but 6 months later a follow-up esophagoscopic examination showed a circumferential ulceration with severe stricture in the same region (**B**). Because she had been taking alendronate sodium weekly to prevent osteoporosis for 2 years before presentation, we recommended it be discontinued. The esophageal ulcer progressively healed (**C**); however, 7 sessions of endoscopic balloon dilation over 6 months were needed to relieve her dysphagia. Clinicians should consider the possibility of adverse effects from alendronate sodium tablets in the appropriate patient with esophageal ulceration.

DISCLOSURE

All authors disclosed no financial relationships relevant to this publication.

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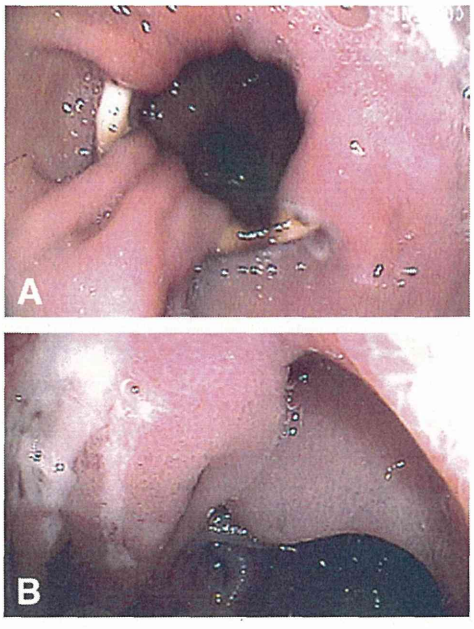
Commentary

Alendronate sodium is a selective inhibitor of osteoclast-mediated bone resorption that increases bone mass, decreases vertebral fractures, and treats postmenopausal osteoporosis. Before its caustic effects on the upper GI tract were well appreciated, it was also the endocrinologist's contribution to endoscopy revenues. In early postmarket studies of alendronate, comprising nearly half a million patients, up to 25% of the drug's reported adverse events were from severe esophageal injury, primarily chemical esophagitis. Biopsy of the involved mucosa often shows polarizable crystalline material and multinucleated giant cells characteristic of pill-related injury. Alendronate should only be taken in the upright position, usually on arising for the day, and with 6 to 8 oz of water. Failure to adhere to this morning ritual may increase the risk of esophageal misadventure. Although this second-generation uncoated monosodium salt was designed, with some success, to maximize solubility and minimize esophageal mucosal adherence, retained tablets still can cause circumferential ulceration focally or throughout the esophagus. Although these changes can be persistent, strictures requiring repeated dilation are rare. What makes this case hard to swallow is the severity of the drug toxicity despite taking it as directed.

David Robbins, MD, MSc,
Assistant Editor for Focal Points

Partially migrated gastric ring after transected banded vertical gastric bypass



A 59-year-old man who had had bariatric surgery 4 years previously presented with maroon stools and dizziness. The patient was taking a nonsteroidal anti-inflammatory drug (NSAID). He was found to have orthostatic hypotension and tachycardia with normocytic anemia (hemoglobin 7 g/dL; normal 14-18 g/dL); blood test results were otherwise normal. EGD revealed a small gastric pouch that led into the small intestine. A ring that had partially eroded through the stomach wall was identified (**A**). The patient previously had a transected banded vertical gastric bypass, during which a silastic ring was placed around the gastric pouch proximal to the gastrojejunal anastomosis. A clean-based ulcer (**B**) also was found on the jejunal side of the anastomosis, without active bleeding or high-risk stigmata. NSAID therapy was discontinued, and the patient began therapy with omeprazole and was discharged.

Efficacy of Preventive Endoscopic Balloon Dilation for Esophageal Stricture After Endoscopic Resection

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Background and Aim: We earlier reported that mucosal defect involving over three-fourths of the circumference of the esophagus after endoscopic mucosal resection (EMR) is a risk factor for the development of the stricture. Although endoscopic balloon dilation (EBD) is a useful procedure to relieve the stricture, there is no standard strategy for preventing development of the stricture. The aim of this study was to evaluate the efficacy and the safety of preventive EBD.

Methods: From 1993 to 2008, 41 consecutive patients with extensive mucosal defect involving over three-fourths of the esophageal circumference after EMR or endoscopic submucosal dissection (ESD) were investigated. Preventive EBD was carried out for 29 cases within 1 week just after EMR/ESD and was repeated once a week until the mucosal defect was completely healed. The remaining 12 cases were not underwent preventive EBD and used as a historic control. If postEMR/ESD stricture developed regardless of preventive EBD, conventional EBD was given repeatedly until the stricture was completely relieved.

Results: Preventive EBD decreased the incidence of stricture (59% vs. 92%, $P = 0.04$), reduced the severity of stricture [(≤ 2 mm; > 2 mm and ≤ 5 mm; > 5 mm) = (1; 2; 14) vs. (4; 4; 3), $P = 0.01$] and shortened the duration required for resolving the stricture (29 d vs. 78 d, $P = 0.04$) even when stricture developed. There was no complication associated with preventive EBD procedure.

Conclusions: Preventive EBD is an effective procedure to prevent postEMR/ESD stricture. Preventive EBD should be considered when EMR/ESD results in a mucosal defect with a circumference greater than three-fourths of the esophageal lumen.

Key Words: endoscopic mucosal resection, endoscopic submucosal dissection, esophageal stricture, endoscopic balloon dilation, prevention

(*J Clin Gastroenterol* 2011;45:222–227)

Endoscopic mucosal resection (EMR) is being increasingly accepted as one of the standard treatment for superficial esophageal cancer because of its minimal invasiveness and excellent survival rate.[1,2] Furthermore, the endoscopic submucosal dissection (ESD) technique has made it possible to carry out *en-bloc* resection of widespread neoplasia, such as a superficial spreading-type of esophageal squamous cell carcinoma and Barrett esophageal cancer.[3–7] However, extended removal of the esophageal mucosa frequently causes severe stricture.[8,9]

Esophageal stricture may markedly interfere with the oral intake of food and fluids, and thus affect the patients' quality of life adversely. In addition, once severe esophageal stricture has developed, it is difficult to resolve the condition. Although endoscopic balloon dilation (EBD) is usually indicated for benign stricture including the cicatricial stricture caused by EMR/ESD, the effect of EBD is sometimes only temporary and the stricture would reappear.[10,11]

Before 2002, we carried out EBD only when the patients complained of dysphagea by postEMR/ESD stricture, and EBD was repeated until the dysphagea was completely resolved. In 2003, we reported that mucosal defects greater than three-fourths of the circumference of the esophagus after EMR are at high risk of developing esophageal stricture.[12] Since then, we started preventive EBD not to develop stricture, before postEMR/ESD mucosal defects develop scarring.

In this study, we evaluated the effectiveness of preventive EBD for the patients with superficial widespread esophageal cancer who developed mucosal defect extending more than three-fourths of the circumference of the esophagus by EMR/ESD.

PATIENTS AND METHODS

Patients

From February 1993 to June 2008, we experienced 64 consecutive patients with widespread mucosal defects greater than three-fourths of the esophageal circumference as a result of EMR/ESD for esophageal cancer. Written informed consent was obtained from all patients before carrying out EMR/ESD and EBD.

Endoscopic Resection Technique

To remove the lesions endoscopically, EMR[13,14] or ESD[5–7] were carried out.

EBD Technique

All patients received administration of 17.5 to 35 mg of pethidine hydrochloride to reduce the suffering from EBD

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procedure. All EBD procedures were carried out using direct visualization and fluoroscopic monitoring. The balloon was positioned across the stenotic site, and then it was inflated carefully with double-diluted contrast agent. During the procedure, patients were closely observed with pulse, blood pressure, and oxygen saturation. When a patient experienced pain during the dilation or when a notch of the balloon placed on the stricture was gradually disappeared, dilation was stopped, and then the balloon was maintained in its inflated state and held close to the tip of the endoscope, and was pushed through the stenotic site as a bougie technique. If the notch of the balloon was rapidly expanded, suggesting a tear at the stenotic site, dilation is immediately stopped and the balloon was deflated, and then the endoscope and deflated balloon were removed.

Four CRE balloon dilators (Boston Scientific Corp. Natick, MA, USA) of different sizes (10 to 12 mm, 12 to 15 mm, 15 to 18 mm, and 18 to 20 mm) were used according to the severity of the stricture. A single balloon was used in each EBD session. When the endoscope could be passed through the site of the mucosal defect, a balloon of 18 to 20 mm was used. When the stricture was less than 10 mm in diameter and larger than 5 mm, a 15 to 18 mm balloon was used. When the stricture was less than 5 mm in diameter and larger than 2 to 3 mm, a 12 to 15 mm balloon was used. When the stricture was a pinhole stricture, a 10 to 12 mm balloon was used. We did not carry out preventive EBD when the luminal diameter was estimated to be greater than 20 mm because the diameter of the lumen would have been greater than that of the fully expanded balloon.

In this study, we defined the EBD procedure carried out immediately after EMR/ESD as "preventive EBD" and that after the development of postEMR/ESD cicatricial stricture as "conventional EBD."

Protocol of the Preventive EBD and Conventional EBD

Preventive EBD was commenced within 1week after the EMR/ESD and repeated weekly until the complete healing of mucosal defect was observed (Fig. 1). Patients consumed a regular diet during the period of mucosal healing and weekly preventive EBD.

If the postEMR/ESD mucosal defects became scarred with stricture despite repeated preventive EBD, conventional EBD was given repeatedly until the stricture was completely resolved. The time interval of conventional EBD depended on patients' symptom such as dysphagea (usually 2 to 4 wk). The strategy of conventional EBD has not been changed throughout this study period, therefore, the time interval of conventional EBD is not different between 2 groups.

Definition of the Stricture

"Stricture" was defined when a standard 11-mm-diameter endoscope (Q240, 1T240; Olympus Optical Co. Ltd., Tokyo, Japan) could not be passed through the site, or when the patients complaint of dysphagea. Whereas, "complete resolution of the stricture" was defined when a standard diameter endoscope could be passed through the site, and patients' symptoms of dysphagia were completely relieved.

In each EBD sessions in all cases, diameter of stricture was measured by comparing with the diameter of inflated balloon under the fluoroscopic monitoring, and it was classed into 3 groups: more than equal to 2 mm; more than 2 mm and, more than equal to 5 mm; more than 5 mm. The duration required for resolving the stricture was defined as the time interval between the day when the stricture was first observed and the day of complete resolution.

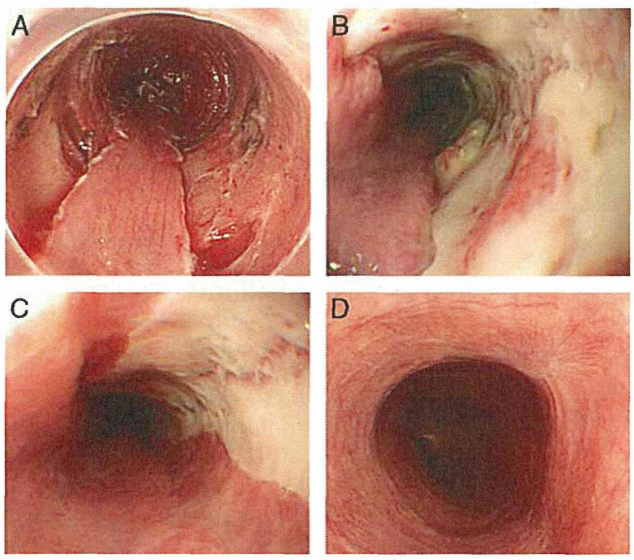

FIGURE 1. A representative case who received preventive endoscopic balloon dilation after a semicircumferential endoscopic submucosal dissection(ESD). A, Semicircumferential mucosal defect immediately after the ESD. B, Mucosal defect 1 week after the ESD. The site gradually developed scarring with mild stricture. C, Mucosal defect 1 month after the ESD. The site developed scarring furthermore, but the stricture was mild. D, PostESD site 2 months after the ESD. The complete healing of the postESD mucosal defect was observed without stricture. The endoscope could be passed through the site and the patient did not complain of any symptom with esophageal stricture.

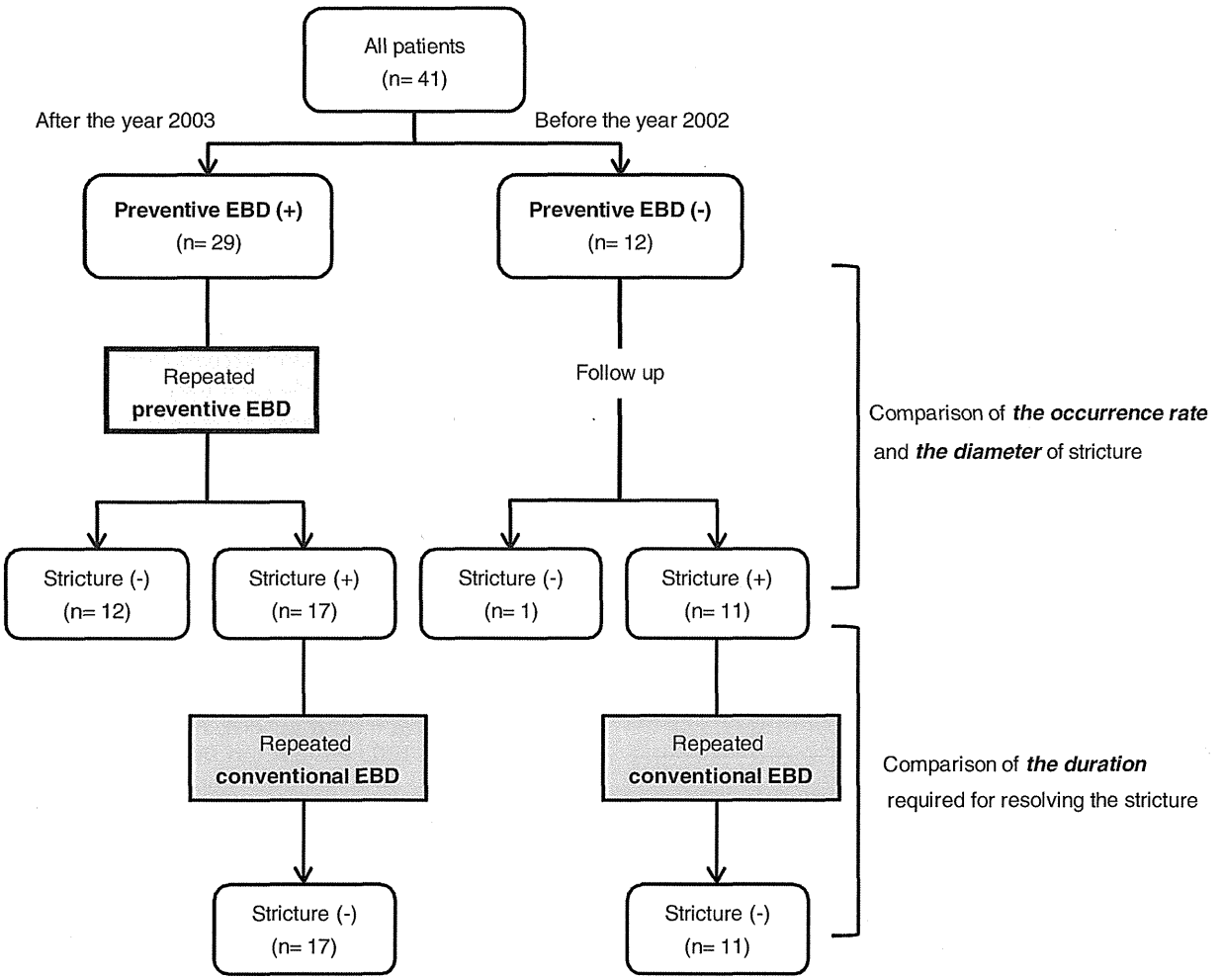

FIGURE 2. Diagram of patients flow.

Evaluation of Preventive EBD

The efficacy of preventive EBD was evaluated retrospectively by comparing the following 3 points between the patients with preventive EBD and those without it (Fig. 2); the occurrence rate of stricture, the diameter of stricture, and the duration required for resolving the stricture by repeated conventional EBD.

Statistical Analysis

Fisher exact test, or its extension when there were more than 2 categories, was used for categorical variables and the Mann–Whitney *U* test was used for continuous variables. Cox proportional hazard model was used for the multivariate analysis. A *P* value of more than equal to 0.05 was considered significant. All statistical analyses were carried out using the Dr SPSS II Statistics software package (SPSS Japan Inc., Tokyo, Japan).

RESULTS

Patient Background

Among the 64 patients with mucosal defects greater than three-fourths of the circumference of the esophagus after EMR/ESD, 3 patients did not attend follow-up consultations, 17 received additional treatment for primary lesions (chemoradiation for deep invasion of the carcinoma or EMR/ESD for local recurrence and incomplete resection), and 3 underwent surgical resection for metachronous gastric cancer immediately after EMR/ESD. We excluded these 23 patients because additional treatments had the potential to make the stricture worse. Finally, we used data from 41 lesions in 41 patients to evaluate the efficacy of the preventive EBD.

Thirty-six lesions were removed by EMR and 5 lesions were removed by ESD procedure. A histopathological diagnosis of squamous cell carcinoma was found in all lesions and 40 lesions were mucosal cancers but 1 submucosal cancer.

Of the 41 patients, 29 underwent preventive EBD and 12 did not. There were no statistical differences in the characteristics of the patients and the mucosal defects except for the endoscopic resection method between patients who underwent preventive EBD and those who did not. Because the ESD was recently established technique, there are no patients treated by ESD in the historical control group. Although the difference was not statistically significant, the rate of circumferential resections tended to be greater in

TABLE 1. Comparison of the Characteristics of Mucosal Defects After Endoscopic Resection in Patients With and Without Preventive EBD

	Preventive EBD		
	(+) n = 29	(–) n = 12	*P*
Sex			
Male	28	11	0.50
Female	1	1	
Age			
Median (range)	64 years (50-74)	60 years (48-80)	0.21
Circumference of the lumen			
Circumferential	10	6	0.49
Semi-circumferential	19	6	
Depth of resected lesion			
Mucosa	28	12	0.34
Submucosa	1	0	
Location			
Upper	3	1	0.30
Middle	13	5	
Lower	13	6	
Length of mucosal defect			
30 mm or less	6	4	0.30
More than 30 mm	23	8	
Median (range)	40 mm (10-110)	45 mm (20-70)	0.38
Endoscopic resection procedure			
EMR	24	12	< 0.001
ESD	5	0	

Number of patients are shown unless specified.
EBD indicates endoscopic balloon dilation; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection.

conventional EBD group [10/29 (34%) vs. 6/12 (50%), $P = 0.49$] (Table 1).

Profile of Preventive EBD Sessions

Among the 29 patients who underwent preventive EBD, the median number of preventive EBD sessions was 6 (range, 3 to 9) and the period of preventive EBD was 45 days (range, 16 to 65) (Table 3).

Efficacy of Preventive EBD

The number of patients who developed stricture after EMR/ESD was significantly lower in patients who were given preventive EBD than those who were not given preventive EBD [12/29 (59%) vs. 11/12 (92%), $P = 0.04$] (Table 2).

TABLE 2. Comparison of the Occurrence Rate and the Diameter of Esophageal Stricture Between Patients With and Without Preventive EBD

	Preventive EBD		
	(+)	(–)	*P*
No. patients who developed stricture	17/29 (59%)	11/12 (92%)	0.04
The narrowest diameter of the stricture			
≤2 mm	1/17 (6%)	4/11 (36%)	0.01
2 mm < and ≤5 mm	2/17 (12%)	4/11 (36%)	
5 mm <	14/17 (82%)	3/11 (28%)	

Number of patients are shown unless specified.
EBD indicates endoscopic balloon dilation.

The narrowest diameter of stricture in each patient was significantly larger in patients who were given preventive EBD than those who were not given preventive EBD [(≤2 mm; >2 mm and ≤5 mm; >5 mm) = (1; 2; 14) vs. (4; 4; 3), $P = 0.01$] (Table 2).

The number of days to development of stricture was 23 days (21 to 49) in patients without preventive EBD. Similarly, in patients who were given preventive EBD, tendency of stricture development was observed within 2 weeks after EMR/ESD. However, preventive EBD could prevent the patients' symptom such as dysphagea because dilation was carried out at short intervals (once a week) in all patients. Therefore, no patients suffered from dysphagea during the preventive EBD period in this study. Since the patients with preventive EBD complained the symptom of dysphagia after the completion of weekly preventive EBD, the number of days to development of stricture was 51 days (30 to 72). It was significantly longer in patients who underwent preventive EBD than those who did not ($P < 0.001$).

Seventeen patients with preventive EBD and 11 patients without preventive EBD developed esophageal stricture. Then, they were given conventional EBD repeatedly until the stricture was completely relieved. Among them, the duration required conventional EBD was significantly shorter in patients given preventive EBD than in those not given it (29 d vs. 78 d; $P = 0.04$). The number of conventional EBD sessions was smaller in patients with preventive EBD than in those without it, although the difference was not statistically significant (2 times vs. 4.5 times; $P = 0.5$) (Table 3).

The number of total EBD sessions was greater in patients with preventive EBD than in those without it, however, the difference was not statistically significant (8 times vs. 4.5 times; $P = 0.42$) (Table 3).

Safety of EBD Procedure

Among a total of 166 preventive EBD sessions for 29 patients, no complication occurred during the procedure (complication rate of preventive EBD: 0%). Among a total of 189 conventional EBD sessions for 28 patients, a perforation was occurred in 1 conventional EBD session in 1 patient (0.5% per total conventional EBD sessions, 3.6% per patient). The patient was immediately hospitalized and administered intravenous antibiotics. The patient had no symptoms or signs of mediastinitis. The fasting period was 3 days and hospital stay was only 1 week after causal EBD. No other major complication occurred.

Clinical Course of all Patients After EMR/ESD

Follow up period was calculated between the day of EMR/ESD and the day of patients' final visit. After the complete resolution of stricture, endoscopic examination was carried out every 6 months in all patients. Median follow up period of all patients was 84 months. There were no patients who suffered from dysphagea owing to the recurrence of stricture.

RISK OF STRICTURE

Risk Factors for Stricture Among Patients With Preventive EBD

The method of EMR and the longitudinal length of mucosal defect (> 30 mm in length) were significantly

TABLE 3. Comparison of the Duration and the Number of EBD Sessions Required for Resolving the Stricture by Conventional EBD Between Patients With and Without Preventive EBD

	Preventive EBD		
	(+)	(−)	*P*
Period of preventive EBD*	45 d (16-65)	(−)	(−)
Number of days to development of the stricture*	51 d (30-72)	23 d (21-49)	< 0.001
Duration required for resolving the stricture*	29 d (15-169)	78 d (8-1093)	0.04
No. preventive EBD sessions*	6.0 sessions (3-9)	(−)	(−)
No. conventional EBD sessions*	2.0 sessions (2-20)	4.5 sessions (2-35)	0.5
No. total EBD sessions*	8.0 sessions (3-29)	4.5 sessions (0-35)	0.42
No. patients whose stricture was relieved	17/17 (100%)	11/11 (100%)	1

Number of patients are shown unless specified.
*Median (range).
EBD indicates endoscopic balloon dilation.

associated with the increased risk for development of stricture by multivariate analysis (Odds ratio: 20.8, 95% CI: 1.3-328.9 and 12.7, 95% CI: 1.3-126.9, respectively). Circumferential mucosal defects showed a higher rate of stricture than semicircumferential mucosal defects; however, the difference was not statistically significant (Odds ratio: 3.0, 95% CI: 0.2-40.5) (Table 4).

DISCUSSION

Technically, extended esophageal mucosal resection could be carried out. However, the development of the esophageal stricture is one of the most important problem to be solved. To date, there are no well-established methods to prevent the stricture after EMR/ESD. If we can prevent the development of the stricture after EMR/ESD by preventive EBD, the ability of the patients oral intake would be dramatically improved.

In this study, we showed that the preventive EBD reduced the incidence of esophageal stricture in patients who underwent an extensive EMR/ESD. In our preventive EBD protocol, EBD was carried out once a week for about 6 weeks [median; 44 days (16 to 65 d)] until the mucosal defect completely developed scar. Because of this strategy, the number of EBD sessions tended to be greater. Although it did not reach statistical significance ($P = 0.42$), the total number of EBD sessions was nearly twice as high compared with the conventional EBD group (8.0 vs. 4.5). However, the narrowest diameter of stricture was significantly mild in the preventive EBD group compared with the group without it (Table 2), whereas 60% of the patients in the preventive EBD group develop stricture. Clinically, the severity of the stricture is very important, because it critically affects the oral intake condition. Furthermore, the preventive EBD shortened the period to relieve the stricture even when the stricture was developed. These data indicated that the preventive EBD was a beneficial method, and thus should be considered to carry out for the patients who underwent extensive EMR/ESD as a supportive treatment.

TABLE 4. Predictive Factors for Development of Stricture After Endoscopic Resection in Patients who Received Preventive EBD

	Odds Ratio (95% CI)	*P*
Method of endoscopic resection		
ESD	1.0 (reference)	0.03
EMR	20.8 (1.3-328.9)	
Longitudinal length of mucosal defect involving over three-fourth of the esophageal circumference		
≤ 30 mm	1.0 (reference)	0.03
> 30 mm	12.7 (1.3-126.9)	
Circumference of mucosal defect		
Semi-circumferential	1.0 (reference)	0.4
Circumferential	3.0 (0.2-40.5)	

EBD indicates endoscopic balloon dilation.

Perforation and massive bleeding were the most severe complications during the EBD procedure. However, there was no complication associated with preventive EBD procedure in this study. Thus, we could conclude that the preventive EBD was a feasible procedure. Not to develop perforation, we carefully carried out preventive EBD under fluoroscopic monitoring, to confirm with both the size of the stricture and the inflated balloon. When the patients complained of pain or when the balloon expanded exponentially, we stopped dilating the balloon immediately not to develop deep tear or perforation.

There were some imbalances of the characteristics of mucosal defect between 2 groups; the rate of circumferential resections [10/29 (34%) vs. 6/12 (50%), $P = 0.49$] and the rate of ESD resections [5/29 (17%) vs. 0/12 (0%), $P < 0.001$]. Although the difference of the rate of circumferential resections was not statistically significant, the possibility that the results of this study might be influenced by the difference cannot be denied. However, the "circumferential resection" and "noncircumferential resection" were not associated with the risk of development of stricture by the multivariate analysis even in the preventive EBD group. Therefore, it seemed that the imbalance about the rate of circumferential resection between 2 groups was not a major problem. As for the different rate of ESD resections, there are no patients treated by ESD in the historical control group because the ESD was recently established technique. These imbalances between 2 groups are unavoidable limitations of the retrospective review with small sample size.

The rate for stricture was lower in patients who underwent ESD than those who received EMR [1/5 (20.0%) vs. 16/24 (66.7%), $P = 0.03$]. Although the reason for this difference is unknown, 1 possibility is that the potent cautery effect of EMR compared with that of ESD might cause more severe submucosal injury resulting in an

increased risk for development of stricture.[15] Clarification of the precise mechanisms for developing stricture after EMR/ESD is warranted in future studies. In addition, the difference of rate for stricture between 2 groups might be influenced by the lower rate for stricture in ESD patients. However, there are no ESD patients who did not undergo preventive EBD, it is therefore impossible to evaluate real influence from ESD patients for the results of this study.

Temporary stent placement may also be a promising strategy for preventing postEMR/ESD stricture. Self-expandable removable stents or biodegradable stents have been reported to be useful for the treatment of benign stricture such as anastomotic stricture and cicatricial stricture by esophagitis.[16] However, there has been no report on the use of self-expandable removable stents for preventing the postEMR/ESD stricture. Although the biodegradable stents have been reportedly applied for prevention of the postEMR/ESD stricture, a small number of patients, short-term follow-up periods, and a high frequency of stent migration obscured its usefulness.[17,18] Thus, further evaluation of these methods is required to compare their usefulness with the EBD.

The multivariate analysis in patients with preventive EBD showed that the longer longitudinal mucosal defects (>30 mm) was the significant risk factor for development of the stricture; in contrast, the circumferential mucosal defect was not a significant risk factor. To avoid the treatment induced esophageal stricture, these data are informative when we select the treatment modalities for the extended esophageal cancer; such as EMR/ESD, chemoradiotherapy, radiotherapy, or surgical resection. If patients prefer the remaining the sufficient ability of oral intake, extensive EMR/ESD should not be indicated, because the long term EBD would be needed and the symptom of dysphagia afflicts the patients.

In conclusion, preventive EBD could be a useful and acceptable strategy to reduce the incidence of postEMR/ESD stricture. Because there is no other effective method to prevent stricture after extensive EMR/ESD at present, preventive EBD should be considered for all patients who undergo extensive EMR/ESD. Although almost 60% of patient developed stricture despite the preventive EBD, the severity of the stricture was clearly reduced even when the stricture was developed. Since the number of patients in this study is rather small, and moreover, this was the retrospective study, a prospective study with a large number of cases is required to confirm the effectiveness of preventive EBD procedure for the prevention of postEMR/ESD stricture in patients with early stage esophageal cancer.

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Early Detection of 5-FU-induced Acute Leukoencephalopathy on Diffusion-Weighted MRI

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A 59-year-old man treated with 5-fluorouracil and cisplatin for advanced oesophageal cancer presented abnormal behaviour and subsequently developed impairment of cognitive function, dysphagia and dysarthria on the fifth day of the treatment. Although brain computed tomography revealed no abnormal findings, brain magnetic resonance imaging using diffusion-weighted imaging clearly revealed the presence of a high signal intensity in the deep white matter of the bilateral cerebral hemispheres, including the corpus callosum symmetrically. A diagnosis of acute leukoencephalopathy was reached based on these findings. His clinical symptoms normalized four days after the discontinuation of the chemotherapy. Improvement in magnetic resonance imaging findings was delayed compared with that of clinical symptoms; however, the high signal intensity detected in the deep white matter had disappeared completely five months after the onset of symptoms. Early detection of drug-induced leukoencephalopathy is important as the clinical symptoms can be reversed by early discontinuation of the causative drug. Diffusion-weighted magnetic resonance imaging is a useful modality for the early detection and definitive diagnosis of this characteristic encephalopathy.

Key words: acute luekoencephalopathy – 5-fluorouracil – oesophageal cancer – MRI – diffusion-weighted imaging

INTRODUCTION

5-Fluorouracil (5-FU) is widely used in the treatment of a spectrum of solid cancers, such as carcinoma of the head and neck, oesophagus, stomach, intestine and ovaries. Some adverse reactions of the drug, which include toxic effects to the central nervous system, have been reported (1,2). Among them, encephalopathy is rare and may present as disorientation, confusion, agitation, neurosensory hearing impairment, seizure, stupor, and even deep coma. Diffusion-weighted magnetic resonance imaging (DW-MRI) is a useful modality for the early detection and definitive diagnosis of this characteristic encephalopathy. Herein, we reported a case of 5-FU-induced acute leukoencephalopathy.

CASE REPORT

A 59-year-old man who presented with cough and dysphagia was admitted to our hospital. Oesophago-gastroduodenoscopy showed an ulcerative and localized type of tumour in the middle oesophagus with intramural metastasis to the anal side. A biopsy specimen revealed the presence of well-differentiated squamous cell carcinoma. Enhanced computed tomography (CT) demonstrated that the oesophageal wall thickness was invasive to the surrounded organs, with multiple lymph nodes metastasis at the supramediastinum and the bilateral supraclavicular fossa and with paraaortic localization. A diagnosis of stage IVB (TNM classification. cT4N1M1b) advanced oesophageal cancer was established

and the patient received systemic chemotherapy (cisplatin, cis-diaminedichloroplatinum (CDDP); 80 mg/m^2, day 1) and 5-fluorouracil (5-FU; 800 mg/m^2, days 1–5). On the fifth day of the treatment, he presented an abnormal behaviour and subsequently developed impairment of cognitive function, dysphagia and dysarthria. Vital signs and serum examination were normal, with the exception of an elevated level of ammonia (117 μg/dl; normal range, 20–60 μg/dl). No abnormal findings, including brain metastasis, were detected in the CT images (Fig. 1) and T1-weighted magnetic resonance imaging (MRI) (Fig. 2A). T2-weighted MRI faintly revealed the presence of a high signal intensity in the deep white matter of the bilateral cerebral hemispheres, including the corpus callosum (Fig. 2B). In contrast, DW-MRI clearly revealed the presence of a symmetrical high signal intensity at the same anatomical location (Fig. 2C). As drug-induced acute leukoencephalopathy was suspected based on these findings, both 5-FU and CDDP were discontinued at a total dose of 6000 and 1300 mg, respectively. Clinical symptoms disappeared after the discontinuance of the drugs. He was discharged on the twenty-first day, without recurrence of central nervous system toxicity. One month after the onset of the disease, he was asymptomatic and neurological examination was normal. In addition, the high signal intensity detected in the deep white matter of the bilateral cerebral hemispheres had almost disappeared, and there were only some remnants of it at the splenium of the corpus callosum (Fig. 3A). MRI performed at five months after the onset of the symptoms revealed the complete disappearance of the high signal intensity in both the bilateral cerebral white matter and the corpus callosum (Fig. 3B).

DISCUSSION

Leukoencephalopathy initially manifests itself as dizziness, numbness, disorientation, memory deficit, confusion, agitation, cognitive impairment and unsteady gait. In severer cases, stupor, seizure, akinetic mutism, and even comas may occur (3). Drug-induced leukoencephalopathy is mainly caused by various chemotherapeutic agents, which include methotrexate, vincristine, ifosfamide, fludarabine, cytarabine, 5-fluorouracil, cisplatin and the interferons (4). Among them, 5-FU has been reported most frequently as a leukoencephalopathy causative agent. 5-FU is a fluorine-substituted analogue of pyrimidine uracil. The main action of this agent is to block DNA synthesis by reducing the formation of thymidine monophosphate via the inhibition of the thymidylate synthetase and incorporation into RNA. 5-FU readily penetrates the blood-brain barrier; however, 5-FU-induced neurotoxicity is uncommon and has an incidence of less than 5% among patients treated with this agent. In general, 5-FU-induced leukoencephalopathy is more common in females and in patients with malnutrition or liver dysfunction (5). Hyperammonemia, lactic acidosis and hypocapnia were found to be parallel to the development of encephalopathy. Interestingly, these abnormalities were not detected in patients who did not develop encephalopathy (6). The specific mechanism that underlies hyperammonemia is unknown; however, several factors, including renal dysfunction, constipation, weight loss and infection, aggravate this condition (7).

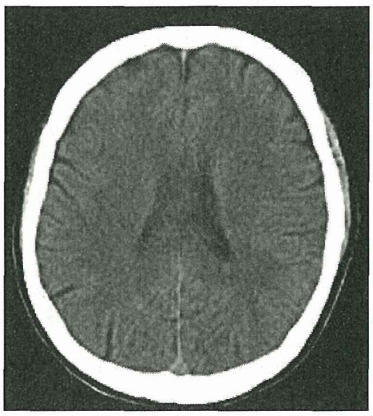

Figure 1. Brain computed tomography performed on the day of the onset of the symptoms showed an absence of abmormalities.

Dyhydropyrimidine dehydrogenase (DPD) is responsible for more than 85% of the catabolism of pyrimidine. Several studies suggest that DPD deficiency, in which the serum and urine levels of uracil and thymidine are increased, may be a risk factor for 5-FU-induced leukoencephalopathy (8).

The common radiological imaging findings of leukoencephalopathy include symmetrical periventricular hypoattenuation on CT scan and diffuse high intensity signal in the white matter and corpus callosum on T2 weighted MRI DW-MRI. DW-MRI is more sensitive than CT scan for the detection of abnormalities in the white matter (9). In the present case, it clearly revealed the presence of a high signal intensity in the deep white matter of the bilateral cerebral hemispheres, including the corpus callosum symmetrically, which was consistent with 5-FU-induced leukoencephalopathy. Cisplatin-induced neurotoxicity is rare and less likely to be present in this case, as the involvement was confined solely to the deep cerebral white matter, and did not extend to the cortex and subcortical white matter (10).

The exact pathological process associated with drug-induced leukoencephalopathy remains unknown. Elevated levels of myelin basic protein in the cerebrospinal fluid (CSF) suggest the presence of myelin destruction (11) (in our case, CSF examination was not performed). *In vitro* and *in vivo* studies suggest that segmental splitting, vacuolization and myelin swelling may occur in humans in the early stage of the disease. It has been known that DW-MRI detects molecular motion of water protons. The accumulation of many small vacuoles within the myelin may interfere with diffusion, thus leading to the appearance of high signal intensity on DW-MRI.

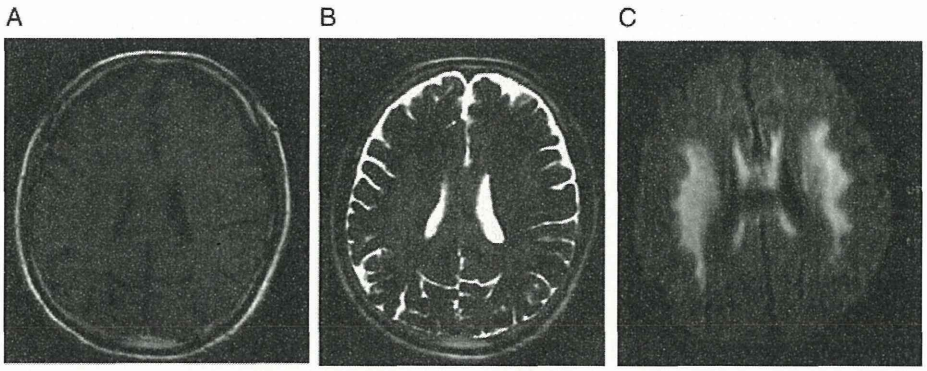

Figure 2. Brain magnetic resonance imaging (MRI) on the day of the onset of the symptoms. (A) No abnormal findings were detected on T1-weighted MRI (B). T2-weighted MRI faintly revealed the presence of a high signal intensity in the deep white matter of the bilateral cerebral hemispheres, including the corpus callosum. (C) In contrast, MRI-diffusion weighted imaging (DWI) clearly revealed the presence of a symmetrical high signal intensity at the same anatomical location. The value of b factor was 1000 s/mm^2.

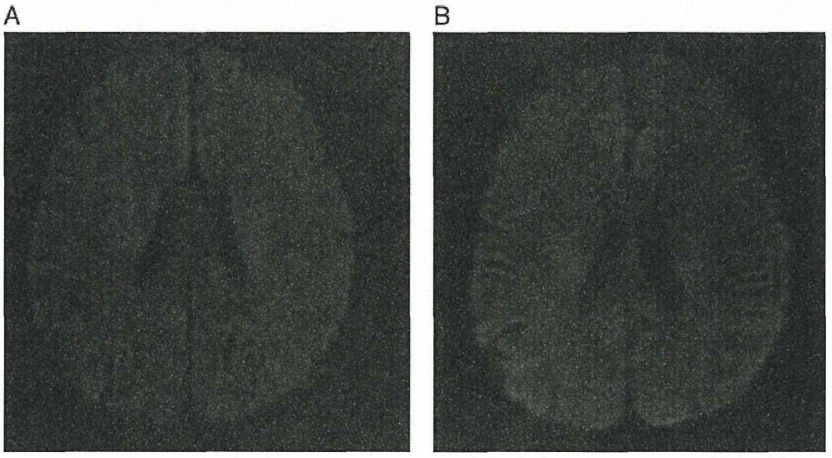

Figure 3. Time course variation of brain MRI-DWI. (A) The high signal intensity detected in the deep white matter of the bilateral cerebral hemispheres and corpus callosum was still slightly visible on MRI-DWI performed one month after the onset of symptoms. (B) These lesions had disappeared completely on the MRI-DWI performed five months after the onset of symptoms.

Drug-induced leukoencephalopathy is dose- and schedule-dependent and is reversible after drug withdrawal or dose reduction; however, in some cases it may lead to life-threatening complications. In other words, the improvement of clinical symptoms after the withdrawal of the causative drug strongly supports the encephalopathy diagnosis. The disease seems to be associated with two clinical courses, according to the time of onset. The first is an acute phase, which develops within one week after administration of the medication. The second is a subacute phase, which develops within five months after administration of the medication (12,13). The treatment modalities proposed in the literature vary considerably and range from purely supportive measures to the use of corticosteroids, thiamine (2,12,13).

Age-related periventricular hyperintensity must be differentiated from drug-induced leukoencephalopathy. Though these T2-weighted MRI findings are similar to those observed in drug-induced leukoencephalopathy, DWI findings differ between the two conditions. DW-MRI of drug-induced leukoencephalopathy revealed the presence of a hyperintensity in the periventricular white matter, whereas that of age-related periventricular hyperintensity showed an absence of any abnormal findings corresponding to the hyperintensity observed on T2-weighted images. From this point of view, DW-MRI seems to be a very useful modality to differentiate this encephalopathy from another condition.

In conclusion, the development of conscious disturbance or abnormal neurological findings in patients treated with chemotherapeutic agents (especially 5-FU) should lead to the consideration of a drug-induced leukoencephalopathy diagnosis. Moreover, in such cases it is important to perform MRI (especially DW-MRI) immediately to establish a

definitive diagnosis, as the neurological symptoms are reversible after discontinuance of the causative drug.

Conflict of interest statement

None declared.

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