CASE REPORT

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Preoperative Iodine Staining May Complicate the Demarcation of Esophageal Carcinoma

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A 53-year-old man was suspected of having an esophageal neoplasm. An endoscopic examination including Lugol chromoendoscopy suggested an esophageal squamous cell neoplasm limited to the lamina propria. A targeted biopsy showed atypical squamous cells, and an endoscopic submucosal dissection was performed 22 days after the previous endoscopy. Although a single 40 mm unstained area was observed by preoperative Lugol chromoendoscopy, intraoperative endoscopy revealed a 25 mm iodine-unstained area, with small unstained areas scattered on the oral side. We included the small unstained areas in the extent of the resection through assessment by preoperative endoscopy. Histopathologically, the tumor extent appeared to coincide with the preoperative assessment. Tumor cells were found in the basal-parabasal layers of the mucosa, in which small unstained areas were scattered, although the superficial layers exhibited well-differentiated cells containing glycogen in the cytoplasm. Although Lugol chromoendoscopy, which can induce chemical esophagitis, is widely used, re-epithelialization after mucosal damage by preoperative iodine staining may complicate the intraoperative demarcation of tumors. **(Gut Liver 2013;7:492-496)**

Key Words: Lugol chromoendoscopy; Esophageal squamous cell neoplasm; Re-epithelialization

INTRODUCTION

Endoscopic submucosal dissection (ESD) has been accepted as an established procedure for superficial esophageal neoplasms.[1] Although the most important advantage of ESD is its effectiveness in resecting lesions regardless of size, postoperative stricture occasionally becomes a problem after ESD for large lesions, especially in the esophagus. To avoid unnecessary complications, an accurate diagnosis of the horizontal extent of the tumor is very important.

At present, Lugol chromoendoscopy is the golden standard for detection and demarcation of esophageal squamous cell neoplasms (ESCN).[2-5] However, it is also reported to occasionally cause mucosal irritation and induce erosions or ulcers in the esophagus.[6,7] We report a case of ESCN in which intraoperative demarcation of tumor became difficult due to re-epithelialization after mucosal damage by preoperative iodine staining. This was confirmed histopathologically after ESD.

CASE REPORT

The patient was a 53-year-old man with no appreciable disease. His alcohol consumption was low (350 mL beer every day) and he did not have a history of smoking. He underwent esophagogastroduodenoscopy as part of a medical checkup and an iodine-unstained area through Lugol chromoendoscopy was pointed out. The next day, he was referred to our institution for further examination. Conventional endoscopy using a high-resolution upper gastrointestinal endoscope (GIF-H260Z; Olympus Medical System Corp., Tokyo, Japan) showed a reddish rough mucosal area on the right side of the middle thoracic esophagus, occupying one third of the circumference of the esophagus (Fig. 1A). The lesion was evaluated as a clearly distinguishable brownish area by narrow band imaging (NBI) endoscopy (Fig. 1B). Dilated and irregular intraepithelial papillary capillary loop (IPCL) pattern was observed in the whole lesion through magnifying endoscopy with NBI. Although elongation of the IPCL was observed partially in the lesion, severe destruction of the

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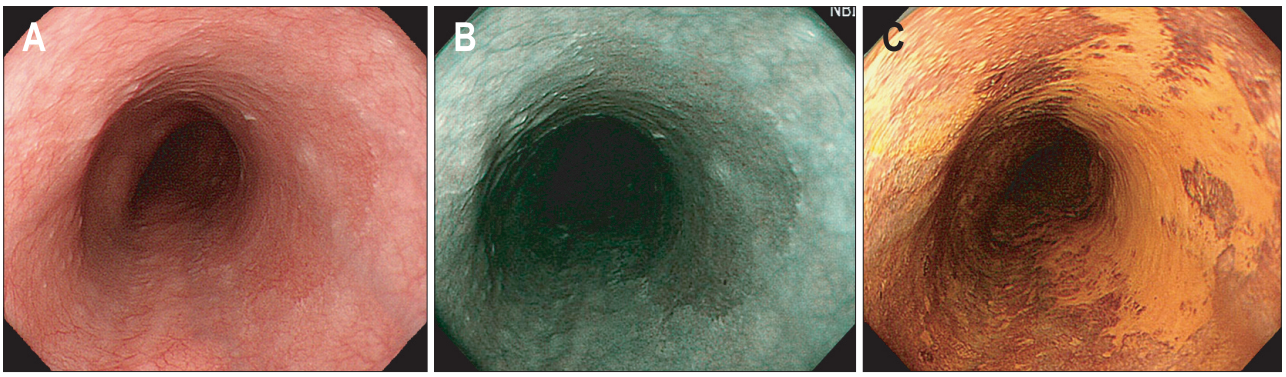

Fig. 1. (A) Conventional endoscopy shows a reddish, rough mucosal area on the right side of the middle thoracic esophagus. (B) The lesion is evaluated as a clearly distinguishable brownish area by narrow band imaging endoscopy. (C) Lugol chromoendoscopy indicates a clearly distinguishable iodine-unstained area measuring approximately 40 mm or less in diameter.

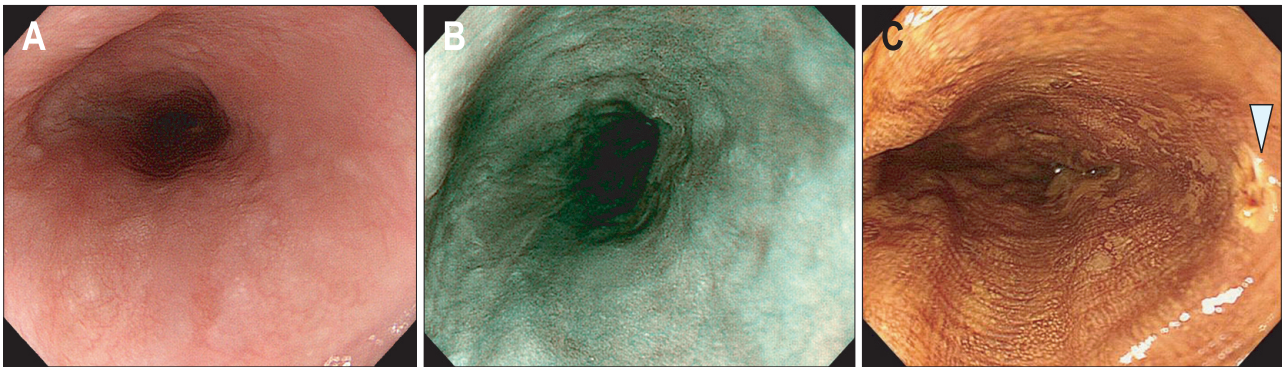

Fig. 2. (A) At the time of treatment, the oral border of the tumor is unclear by conventional endoscopy. (B) The lesion is observed as a brownish area with a vague border and can only be barely demarcated by magnifying endoscopy with narrow band imaging. (C) Intraoperative iodine staining reveals a 25 mm iodine-unstained area and many other small unstained areas scattered on the oral side. The marking (white arrowhead) corresponds to the oral margin of the iodine-unstained area, which was observed by preoperative endoscopy.

vessels was not observed. These findings suggested that it was either high grade intraepithelial neoplasia or invasive squamous cell carcinoma limited to the lamina propria.[8] After noninvasive observation, 20 mL of 3% Lugol's solution was applied on the esophageal mucosa. The lesion was identified as a clearly distinguishable iodine-unstained area measuring about 40 mm or less in diameter (Fig. 1C). A targeted biopsy from the center of the lesion was performed, and the histopathological assessment was atypical squamous cells suggesting squamous cell carcinoma. Computed tomography showed no lymph node metastasis or distant metastasis. Thus, the tumor was thought to be a candidate for ESD.

ESD was performed 22 days after the previous endoscopy. GIF-H260Z was used for evaluation of the horizontal extent of the tumor and marking, and GIF-Q260J for resection of the tumor, respectively. At the time of treatment, the oral border of the tumor was unclear by conventional endoscopy although we used the same endoscope, GIF-H260Z, as in the previous endoscopy (Fig. 2A). The lesion was observed as a brownish area with a vague border and could be barely demarcated by magnifying endoscopy with NBI (Fig. 2B). After that, intraoperative iodine staining with 3% Lugol's solution was performed, and it revealed a 25 mm unstained area as well as many other small unstained areas scattered on the oral side (Fig. 2C). We put marking dots around the identified tumor border including small unstained areas with a 5 mm margin at 2 to 3 mm interval by Dual knife (Olympus Medical System Corp.) because they seemed to concur with the brownish area identified through magnifying endoscopy with NBI and also with the iodine-unstained area observed in the preoperative endoscopy. The ESD procedure was carried out as described previously (Fig. 3).[9]

Histopathological assessment revealed proliferation of atypical squamous cells limited to the mucosal epithelium, indicating high-grade intraepithelial neoplasia. The tumor size was 35 mm in diameter. Both lateral and vertical margins were tumor-free, and there was no vessel infiltration. The extent of tumor cells seemed to coincide with the preoperative assessment (Fig. 4). Tumor cells were also found in the basal-parabasal layers of the mucosa where small unstained areas were scattered, although superficial layers showed well-differentiation containing glycogen in cytoplasm.

The patient was discharged from the hospital 9 days after

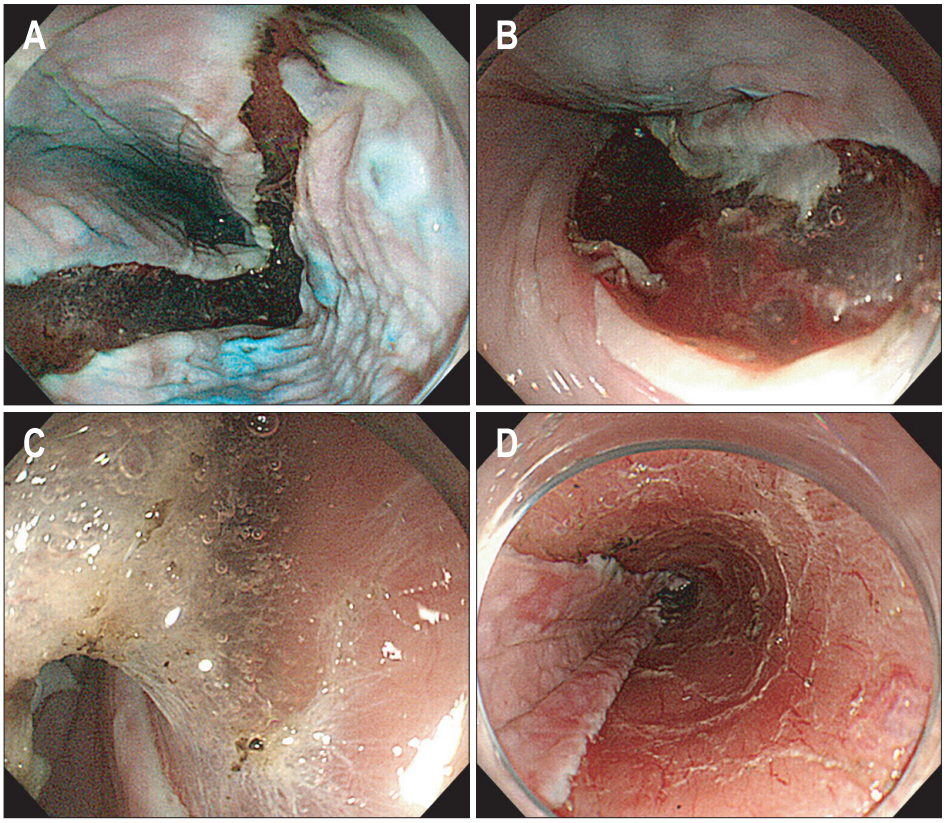

Fig. 3. (A) Mucosal incision made around the marking dots. (B, C) Dissection of the submucosa from the oral end to the anal end. (D) Artificial ulcer after removal of the lesion.

treatment without any complications. He was pathologically judged to be completely cured, and follow-up endoscopy has detected neither local recurrence nor metachronous lesion so far.

DISCUSSION

Since the 1960s when Lugol's solution was first used to evaluate esophageal diseases,[10] it has been widely used in the detection and demarcation of superficial esophageal neoplasms. Targeted biopsies using Lugol chromoendoscopy is now an orthodox procedure. Lugol chromoendoscopy is based on a chemical reaction between iodine, and the glycogen contained in normal epithelial cell microgranules in the stratum spinosum.[11] Dysplastic and cancerous cells are not stained by Lugol's solution because they do not contain glycogen. For this reason, it is reported that endoscopic screening with Lugol's solution is useful for the detection of superficial ESCN in high risk populations, such as patients with a history of head or neck cancers.[2-4] Additionally, Lugol chromoendoscopy has also been reported to be beneficial in the evaluation of horizontal extent of these lesions,[12] and is often used to determine the extent of resection during ESD.

On the other hand, Lugol's solution often causes mucosal irritation leading to retrosternal discomfort.[6] In addition, it is reported to cause chemical esophagitis and gastritis and to induce erosions and ulcers.[7,13,14] Sreedharan *et al*.[14] reported that the biopsies from gastric mucosa of chemical gastritis due to Lugol's solution confirmed acute edema of the lamina propria with loss of the superficial epithelium. We speculate that the same phenomenon occurs in patients with chemical esophagitis.

In this case, mucosal damage by preoperative Lugol chromoendoscopy may have complicated intraoperative demarcation of tumor. At the time of treatment, the unstained area observed in preoperative Lugol chromoendoscopy showed morphological change. A part of the previously unstained area showed an affinity to Lugol's solution, and consequently a 25 mm unstained area with many small unstained areas scattered on the oral side could be observed. Histological assessment of this area revealed atypical squamous cells in the basal-parabasal layers of the mucosa although superficial layers showed well-differentiation containing glycogen in cytoplasm. These results suggested that a portion of atypical squamous cells in the superficial layers desquamated because of the damage by preoperative Lugol chromoendoscopy, and re-epithelialization with normal squamous epithelial cells occurred there, then morphological change of iodine-unstained area was observed at the time of treatment.

An accurate demarcation of tumors is very important especially for esophageal ESD. Lesions should be resected with necessary and sufficient tumor-free margins to minimize local recurrence and unnecessary stricture. To minimize the influence of preoperative Lugol chromoendoscopy, following points may have to be taken into consideration.

First, the concentration of Lugol's solution is an important

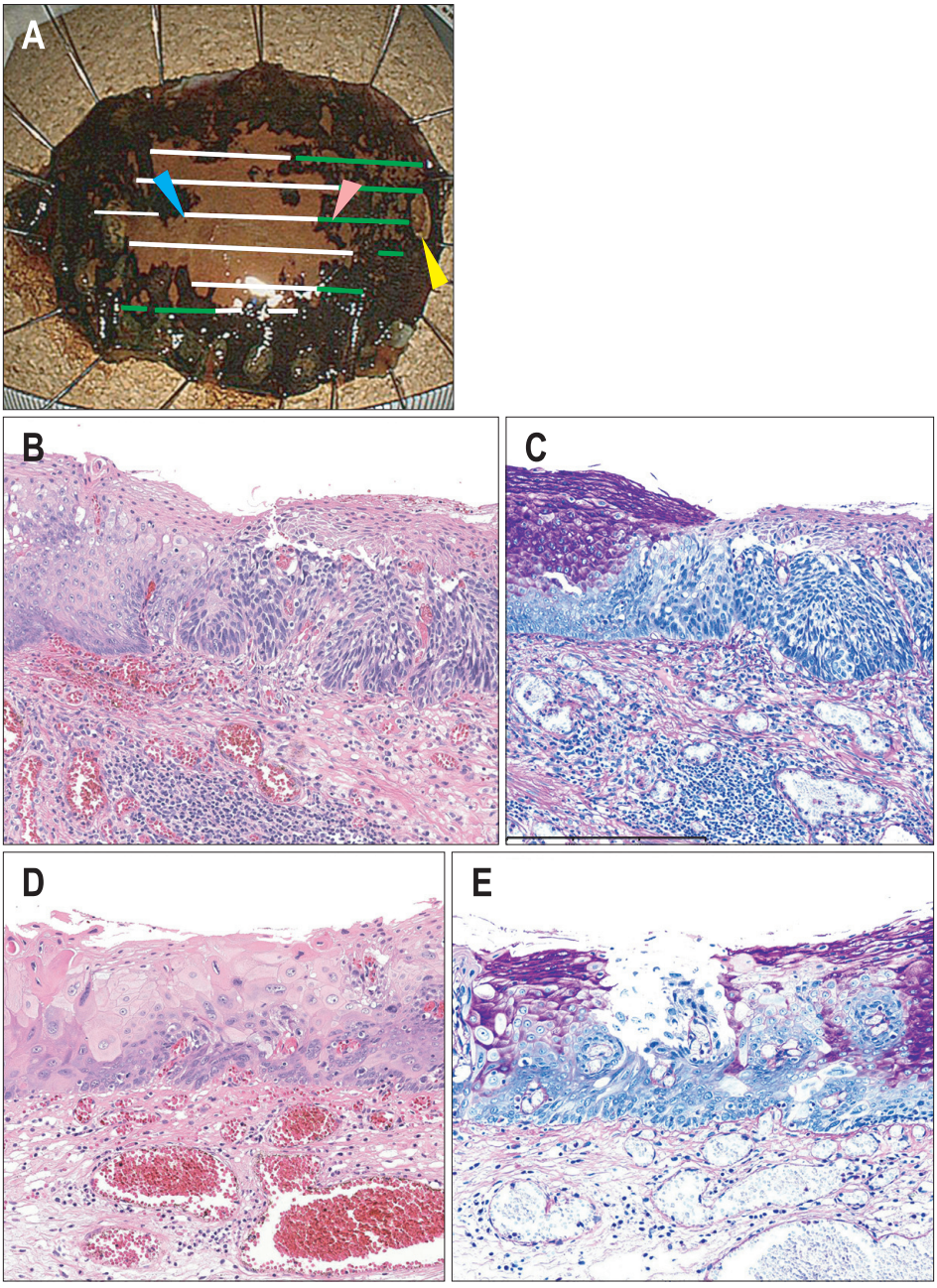

Fig. 4. (A) Histopathologically, atypical squamous cells spread to the mucosa, in which small unstained areas are scattered. The white lines correspond to the main iodine-unstained area. The green lines correspond to the mucosa, in which small unstained areas are scattered. The yellow arrow corresponds to the white arrow in Fig. 2C. Histological images of (B) hematoxylin-eosin and (C) periodic acid-Schiff staining, demonstrating the border area between the atypical squamous epithelium and the non-neoplastic squamous epithelium (blue arrowhead in Fig. 4A, ×100). Atypical squamous cells are not stained by the periodic acid-Schiff stain, corresponding to the main iodine-unstained area. Histological images of (D) hematoxylin-eosin and (E) periodic acid-Schiff staining, demonstrating the mucosa in which small unstained areas were observed by intraoperative iodine staining (pink arrowhead in Fig. 4A, ×100). Atypical squamous cells are found in the basal-parabasal layers, although the superficial layer presents well-differentiated cells containing glycogen in the cytoplasm.

factor. Considering that Lugol chromoendoscopy is based on a chemical reaction, large amounts of free iodine may increase the mucosal damage. Avoiding the usage of high concentration of Lugol's solution may be helpful. Sreedharan *et al*.[14] reported that higher concentrations (3% to 5%) of Lugol's solution might be associated with a higher risk of complications. For the same reason, routine use of sodium thiosulfate solution soon after Lugol chromoendoscopy may theoretically be effective. Kondo *et al*.[6] reported that spraying 20 mL of 5% sodium thiosulfate solution could neutralize free iodine and reduce side effects of Lugol's solution.

Second, the interval from preoperative endoscopy with iodine staining to endoscopic treatment is another important factor. In this case, demarcation of the tumor was clear at first endoscopy in our hospital although he had undergone Lugol chromoendoscopy in another hospital the previous day, indicating that re-epithelialization did not occur immediately after Lugol chromoendoscopy. On the other hand, a sufficient interval from preoperative endoscopy to endoscopic treatment may also be helpful because tumor cells in the basal-parabasal layers of the mucosa is hypothesized to proliferate and replace well-differentiated cells in the superficial layer along with time. However, setting too long interval is a risk for leading tumor progression and resulting noncurative resection by ESD. Further researches are needed to determine the optimal interval from preoperative endoscopy including Lugol chromoendoscopy to endoscopic

treatment.

Magnifying endoscopy with NBI has recently been reported to be useful in the detection of ESCN.[5,15,16] I-scan, which is another image enhanced endoscopy (IEE) technology, has also been reported to be helpful in the detection and the demarcation of gastrointestinal tumors including ESCN.[17] If the progress of these new IEE technologies makes it possible for endoscopists to detect ESCN and to diagnose the horizontal extent of ESCN without spraying Lugol's solution in preoperative endoscopy, the problem of re-epithelialization at the time of treatment may be resolved. However, further studies are required to compare the diagnostic ability of these new technologies and Lugol chromoendoscopy in detecting and demarcating ESCNs.

We encountered a case of ESCN where demarcation of the tumor was complicated by preoperative Lugol chromoendoscopy. Detailed evaluation about the optimal concentration of Lugol's solution and interval from preoperative endoscopy to endoscopic treatment, and further studies about diagnostic ability of IEEs are desirable.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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