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Case Report

Recurrence after Endoscopic Curative Resection of Mucosal Gastric Cancer Associated with an Adjacent Neoplastic Precursor Lesion

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A 69-year-old man underwent endoscopic submucosal dissection (ESD) for early gastric cancer (EGC) at the lesser curvature in the angle of stomach. Histological examination revealed tub1, pM, ly0, v0, pLM(-), pVM(-), and the resection was considered curative. The scar after ESD was followed by esophagogastroduodenoscopy (EGD) and biopsy. Twenty months later, EGD showed an ulcerative lesion in the vicinity of the ESD scar, and histological examination of the biopsy specimen showed adenocarcinoma. A distal gastrectomy with lymph node dissection was then performed. Postoperative pathology showed tub1, pM, pN0, ly0, v0, and Stage 1A. Skip lesions were seen in the specimen resected by ESD, and the histological review confirmed so-called "dysplasia-like atypia" (DLA) between the lesions. It has been reported recently that in DLA, the dysplasia-like change involves only the bases of the pits, without upper pit or surface epithelium involvement, and it is said that the rate of DLA is higher in gastric cancer patients. We speculated that a precancerous lesion close to the resected cancer developed into a local recurrence.

Key words: dysplasia-like atypia, early gastric cancer, endoscopic submucosal dissection, local recurrence

Endoscopic submucosal dissection (ESD) is widely accepted in the treatment of early gastric cancers (EGCs) when lymph node metastasis is negligible [1-3]. Since ESD is less invasive and able to preserve the entire stomach, patients' postoperative quality of life is maintained. In the case of curative resection judged by the Japanese Gastric Cancer Treatment Guidelines [4], local or metastatic recurrence are extremely rare. The incidence rate of local recurrence has been reported to be 0-0.4% [5-7].

We report a case of local recurrence after curative ESD of mucosal EGC. In this case, histological examination showed dysplasia-like atypia (DLA) close to the cancer in the specimen resected by ESD. It has been reported that the dysplasia-like change in DLA involves only the bases of the pits, not the upper pit or surface epithelium. Some studies have reported that in DLA, the neoplastic precursor lesion is located close to the cancer [13-15]. This suggests

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that local recurrence may arise from DLA after curative resection of ESD.

Case Report

A 69-year-old man as part of his annual screening underwent an upper gastrointestinal series that detected an abnormality in the stomach. EGD revealed a slightly elevated lesion, 50 mm in diameter, at the lesser curvature in the angle of stomach, and biopsy indicated a well-differentiated adenocarcinoma (Fig. 1A). There were no specific findings on physical examination or laboratory data, including tumor markers. Endoscopic ultrasound showed the lesion to be confined to the mucosa. On preoperative computed tomography (CT), there were no swollen lymph nodes or distant metastases. ESD was performed on this lesion, resulting in an en bloc resection (Fig. 1B). Pathological examination revealed 2 well-differentiated adenocarcinomas, 17 mm and 6 mm in size, respectively (Fig. 1C, red lines). Both cancer lesions were surrounded with dysplasia-like lesions (Fig. 1C, yellow lines), and these cancer lesions were confined to the mucosa, without lymphovascular involvement. The lateral and vertical margins were negative for both cancer and dysplasia-like lesion invasions, so it was judged that the resection was curative based on standard criteria. The tumors were, however, surrounded by atypical glands as seen in dysplasia. Follow-up EGD examinations were performed every 3-6 months. A small ulcer was detected at the center of the ESD scar and a slightly elevated lesion was found near the ESD scar, but there was no evidence of malignancy on histological examination of the biopsy specimen. Twenty-one months after ESD, EGD revealed a small ulcerative lesion in the center of the ESD scar, and biopsies of the slightly elevated lesions around the ulcerative lesion indicated well-differentiated adenocarcinoma (Fig. 2). Repeated ESD for this relapse lesion was considered technically difficult because of severe fibrosis in the submucosal layer at the site of the initial ESD. Distal gastrectomy with lymph node dissection was performed, and histological examination of the resected stomach revealed adjacent to the initial ESD scar a well-differentiated adenocarcinoma, 50 × 42 mm in size, that was restricted to the mucosa without lymphovascular involvement or lymph node metastasis.

The primary sections that were dissected by ESD were reviewed retrospectively. There were cytologic and architectural atypia of the glands at the bases, confirming that DLA was present close to the cancer lesions at the time of initial resection (Figs. 1C, 3A, 3B). Immunohistochemical staining for Ki-67 was also performed, and Ki-67-positive cells were present at higher levels where there were architectural atypia of the glands (Fig. 3C) than where conventional intestinal metaplasia (IM) existed. During the 3-year follow-up period in this patient, there was no evidence of recurrence.

Discussion

ESD is widely accepted for the treatment of EGC

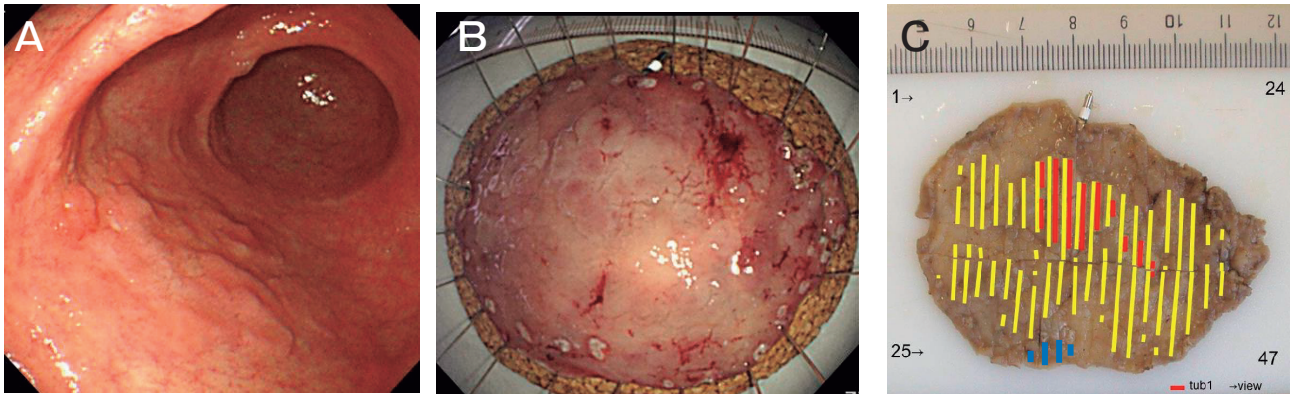

Fig. 1 (A) Esophagogastroduodenoscopy shows a slightly elevated lesion (0-IIa), 50 mm in diameter, at the lesser curvature in the angle of stomach. (B) En bloc resection of the specimen. (C) Tumor mapping shows two cancer lesions (red lines) among dysplasia-like lesions (yellow lines). Retrospectively, the DLA was confirmed close to the cancer lesions (blue line).

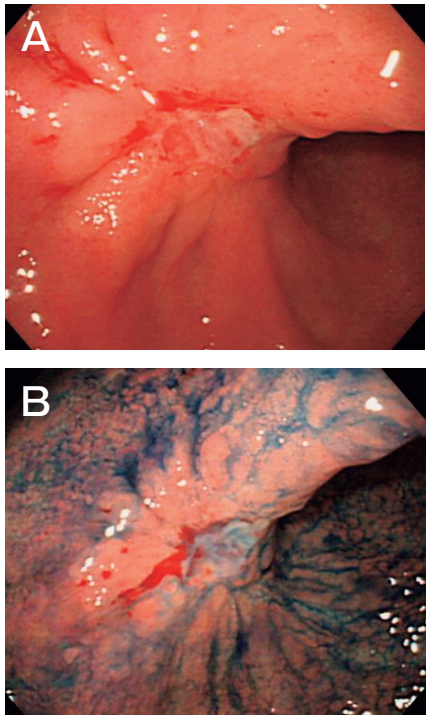

Fig.2 (A), (B) Esophagogastroduodenoscopy shows a small ulcerative lesion in the center of the ESD scar 21 months after ESD. After indigo carmine dye spraying, it can be seen more clearly.

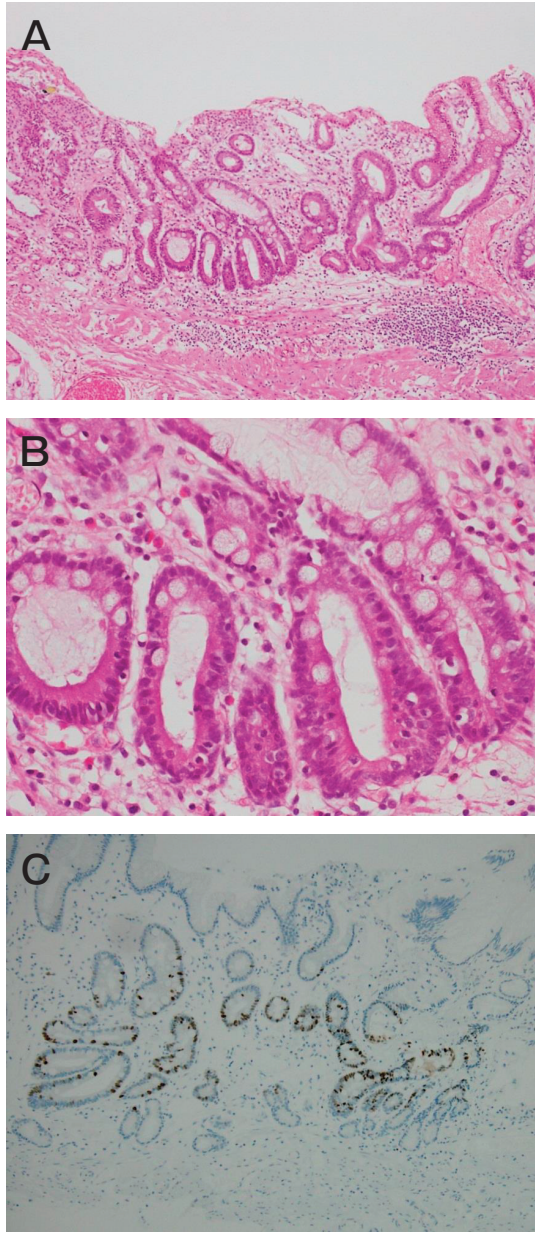

Fig. 3 (A), (B) Histological examination shows that the features of DLA—nuclear elongation, hyperchromatism, and pseudostratification—are present close to the cancer lesion. They are limited to the bases of the gastric pits, without surface involvement. H & E stain. (C) Immunohistochemical staining for Ki-67 in DLA. Ki-67-positive cells are present at higher levels in the pit.

when lymph node metastasis is negligible [1-3]. ESD is less invasive and able to preserve the entire stomach, allowing patients to maintain their quality of life postoperatively. When the lesion is completely resected and judged to be a curative resection according to the Japanese Gastric Cancer Treatment Guidelines [4], the local recurrence rate has been reported to be 0-0.4% [5-7]. In cases of local recurrence, although rare, it has been unclear whether these lesions coincidentally developed near the ESD scar or were residual. It is known that EGC is often accompanied by synchronous or metachronous multiple gastric cancers [1, 8, 9]. Kato *et al.* [7] reported that about 14% of the patients who underwent ESD had multiple gastric cancers, and about 19% of concomitant lesions were missed by preoperative endoscopic evaluation. The miss rate was associated with the experience of the endoscopist and the location of the missed cancers. In the current case, the local recurrence arose in the angle of stomach, which is relatively easy to observe, and multiple preoperative endoscopic evaluations were performed by experienced endoscopists. A concomitant lesion was unlikely to have been missed in this endoscopic survey.

Most intestinal-type gastric cancers are considered to develop through an intestinal metaplasia (IM)-

dysplasia-carcinoma pathway [10, 11]. In this case, it was retrospectively found that the primary lesion that was dissected by ESD was surrounded by mucosa with DLA. The term "Gastric DLA" was described by Brien in 2001; its pathological features are atypical changes present in the foveolar and glandular epithelium in a discontinuous or patchy fashion, surface maturation, an open nuclear chromatin pattern with prominent nucleoli, retention of nuclear polarity, and mitoses confined to the pits [12]. They defined gastric DLA as a non-neoplastic lesion. However, Agoston *et al.* [13] and others [14, 15] recently reported that the rate of DLA was higher in gastric cancer patients than in control patients without gastric cancers, and DLA showed a higher Ki-67-positive rate than intestinal metaplasia. Furthermore, Ki-67-positive cells were present at higher levels in the pit with DLA than with intestinal metaplasia. They concluded that DLA represents an important precursor lesion in gastric carcinogenesis. In the present case, cytologic and architectural atypia of the glands at the bases were histologically confirmed close to the cancer lesions, and Ki-67-positive cells were present at higher levels where architectural atypia of the glands existed, corresponding to DLA. Conventional dysplasia was also confirmed in the initial resected specimen. This suggests that both the remnant DLA and dysplastic lesions close to the resected initial gastric cancer contributed to the carcinogenesis.

Conclusion

Although local recurrence after curative ESD for early gastric cancer is extremely rare, remnant DLA lesions close to the cancer lesion can cause recurrence. Physicians must keep DLA in mind as a precursor neoplastic lesion in gastric carcinogenesis. Needless to say, careful follow-up is mandatory, even after curative ESD.

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