Unusual Local Recurrence with Distant Metastasis after Successful Endoscopic Submucosal Dissection for Colorectal Mucosal Cancer

Hyo Jeong Lee¹, Byong Duk Ye², Jeong-Sik Byeon², Jihun Kim³, Young Soo Park³, Yong Sang Hong⁴, Yong Sik Yoon⁵ and Dong-Hoon Yang²

¹Health Screening and Promotion Center, Departments of ²Gastroenterology, ³Pathology, ⁴Oncology, and ⁵Colon and Rectal Surgery, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea

INTRODUCTION

Colorectal cancer (CRC) with invasion limited to the lamina propria (LP) is defined as intramucosal carcinoma. The current consensus is that intramucosal CRC should not metastasize because colonic LP lacks lymphatics.¹ Hence, intramucosal CRC is classified as “Tis” in the tumor, node, metastasis (TNM) staging system, and endoscopic resection is regarded as adequate treatment.²,³ However, recent reports have described local recurrence with distant metastasis after surgical resection for poorly differentiated intramucosal rectal cancer.⁴ Data regarding metastasis in intramucosal tumors are still lacking, and the metastatic potential of intramucosal CRC remains unclear.

Herein, we report two rare cases of local recurrence with distant metastasis in patients who previously underwent endoscopic submucosal dissection (ESD) for intramucosal CRCs.

CASE REPORTS

Case 1

A 67-year-old woman underwent ESD for a 5.6-cm mixed-nodular type laterally spreading tumor (LST) in the rectum (Fig. 1A, B). Neither a non-lifting sign nor significant submucosal fibrosis was identified. The specimen was fixed in 10% formalin, paraffin-embedded, and evaluated after being cut into 2-mm-thick slices. The histology showed a well-differentiated adenocarcinoma confined to the LP without lympho-vascular invasion and with clear resection margins (Fig. 1C). Abdomino-pelvic computed tomography (CT) did not show any lymph node or distant metastasis. Follow-up sigmoidoscopy at 8 months showed only a scar (Fig. 1D). However, she was admitted with sacral area pain at 17 months after ESD.
Sigmoidoscopy showed an extrinsic infiltrative lesion at the previous ESD site (Fig. 1E). CT showed a perirectal mass, enlarged perirectal lymph nodes, and multiple lung nodules. The pathological findings of the previous ESD site lesion revealed a poorly differentiated adenocarcinoma under normal colonic crypts (Fig. 1F). This undermining invasion pattern without surrounding mucosal change suggested that the recurrent lesion represented in situ recurrence rather than de novo cancer. The histology of lung nodules (Fig. 1F, inset) showed a poorly differentiated adenocarcinoma that was positive for cytokeratin 20 and negative for cytokeratin 7 on immunohistochemistry, suggesting pulmonary metastasis of enteric type adenocarcinoma. Following these findings, the entire original ESD specimen was re-examined after slicing the paraffin-embedded blocks to check for the presence of missed submucosal invasive foci smaller than 2 mm, the routine slice thickness for histologic review of an ESD specimen at our center. At low magnification, the bulky, laterally spreading adenoma contained multiple foci of adenocarcinoma component (Fig. 1C). Higher magnification of the least differentiated area showed solid and cribriform architecture and multiple foci of the invasive front, consisting of small, infiltrative tumor glands (arrowheads) (inset: H&E stain, ×200).

Case 2
A 62-year-old woman underwent en bloc ESD for a 6-cm, mixed-nodular LST in the ascending colon (Fig. 2A, B). No submucosal fibrosis was identified during ESD. The histological examination showed a laterally spreading adenoma with a small fraction of moderately differentiated adenocarcinoma component (Fig. 2C, dashed line). At higher magnification, the invasive tumor cells formed large, irregularly shaped tubules and had occasional goblet cells, and the surrounding stroma was desmoplastic (Fig. 2C, inset). The adenocarcinoma component was confined to the LP without lymphovascular invasion. As expected in the endoscopic findings (Fig. 2B, arrowheads), the resection margins showed severe cautery artifact and low-grade dysplasia involved the resection margins.
Abdomino-pelvic CT did not show any lymph node or distant metastasis. Follow-up colonoscopy at 12 months showed only a scar (Fig. 2D).

However, the patient was admitted with abdominal pain at 34 months after ESD. Colonoscopy showed an ulcerofungating mass encircling the lumen at the previous ESD site (Fig. 2E). Positron emission tomography showed a 1.1-cm hypermetabolic mass in the liver. She underwent right hemicolectomy with hepatic segmentectomy. The colectomy specimen showed a large subserosal tumor with atypical ulcer, which was characterized by the absence of surrounding hyperplastic mucosa and multiple foci of intervening non-neoplastic mucosal islands. Microscopically, the colectomy specimen showed an “undermining” invasion pattern, in which total tumor volume was disproportionately larger than that expected from the size of the mucosal lesion. Furthermore, surrounding mucosa and mucosal “islands” in the ulcer base did not show any preneoplastic changes (Fig. 2F). At higher magnification, the cytomorphology of the resected tumor was similar to that of the invasive component of the previous ESD specimen (Fig. 2F, inset). The pathological findings of the hepatic segmentectomy specimen showed findings similar to those of the colon specimen, suggesting hepatic metastasis from the colon cancer. Similar to case 1, the entire ESD specimen was reviewed again with additional sections of the paraffin-embedded blocks and with CD34 and D2-40 immunostaining. However, submucosal invasive foci and lymphovascular invasion were not identified.

We concluded this case was a recurrence of colon cancer with hepatic metastasis in a patient who previously underwent ESD for intramucosal colon cancer, because the second colon lesion developed precisely at the previous ESD scar site during a 34-month follow-up period, and the pathologic finding showed an “undermining” invasion pattern without surrounding preneoplastic mucosal change.

**DISCUSSION**

Generally, it is thought that intramucosal CRC does not
Table 1. Summary of Case Reports about the Recurrence or Metastasis from Intramucosal Colorectal Adenocarcinoma

| Study                        | Age/Sex | Site     | Size | Initial treatment | Pathology                                                                 | Metastasis at diagnosis | Recurrent lesion       | Interval between treatment and recurrence | Diagnostic tests for recurrence/metastasis |
|------------------------------|---------|----------|------|-------------------|---------------------------------------------------------------------------|------------------------|-----------------------|---------------------------------------------|--------------------------------------------|
| Shia et al. (2008)¹          | 74 yr/M | Rectum   | 4 cm | LAR               | Focal intramucosal adenocarcinoma arising in an adenoma with HGD No metastasis in 8 LNs | None                   | Rectum, omentum, liver | 17 mo                                       | Not mentioned                             |
| Seo et al. (2011)⁰           | 64 yr/M | Rectum   | Not mentioned | En bloc ESD | 2 Synchronous WD adenocarcinomas with LP invasion Clear resection margin | None                   | Perirectal LNs             | 30 mo                                       | CT scan                                   |
| Lee et al. (2014)⁰           | 71 yr/M | SC       | Not mentioned | Laparoscopic AR | 2 Synchronous MD adenocarcinomas with LP invasion No lymphovascular invasion Clear resection margins No metastasis in 9 LNs | Common hepatic LN (1.3 cm at diagnosis, 3.4 cm at 5 mo later, 6.6 cm at 8 mo later) | NA                                   | NA                           | Serial CT scans and excision of the metastatic LN |
| Case 1 of the present report | 67 yr/F | Rectum   | 5.6 cm | En bloc ESD       | WD adenocarcinoma with LP invasion No lymphovascular invasion Focal least differentiated area Clear resection margin | None                   | Rectum (ESD site), lung, perirectal LNs | 17 mo                                       | Colonoscopy, CT scan, and PET             |
| Case 2 of the present report | 62 yr/F | AC       | 6 cm  | En bloc ESD       | MD adenocarcinoma with LP invasion No lymphovascular invasion Margin involvement by LGD | None                   | AC (ESD site), liver      | 34 mo                                       | Colonoscopy, CT scan, and PET             |

LAR, low anterior resection; HGD, high grade dysplasia; LN, lymph node; ESD, endoscopic submucosal dissection; WD, well differentiated; LP, laminar propria; CT, computed tomography; SC, sigmoid colon; AR, anterior resection; MD, moderately differentiated; NA, not applicable; AC, ascending colon; LGD, low grade dysplasia; PET, positron emission tomography.
reduce local recurrence after rectal cancer surgery.\textsuperscript{11} Moreover, a recent study revealed that tumor cells can be exfoliated into the intestinal lumen during colorectal ESD,\textsuperscript{12} although little is known about the clinical significance of exfoliated tumor cells related to endoscopic procedures. Interestingly, a case report suggested that colorectal adenocarcinoma cells might be implanted into the artificial ulcer after endoscopic resection.\textsuperscript{13} As ESD for our primary lesions needed prolonged time, neoplastic cells shed from the tumor surface during the procedure might be implanted on the exposed submucosal layer or directly into the damaged lymphatics of the artificial ulcer. In case 2, which showed lateral margin involvement by adenoma and severe cautery artifact, the remaining neoplastic cells at the margins might be the source of recurrence, although the progression to invasive cancer was extraordinarily fast. The presence of missed unfavorable histologic findings such as focal deep submucosal invasive cancer, even after meticulous histologic reexamination, might be another mechanism of recurrence. The presence of an extremely rare, but still unknown subtype of intramucosal CRC cannot be excluded.

In conclusion, we report two rare cases of local recurrence with distant metastasis in patients who previously underwent successful ESD for intramucosal CRC. Regardless of the mechanism, the rare possibility of recurrence may be considered during surveillance after en bloc ESD of huge intramucosal CRCs. The appropriate surveillance interval after ESD of huge intramucosal CRCs is still uncertain, as most postpolypectomy surveillance guidelines are based on the data retrieved from non-ESD-related studies.\textsuperscript{14-16} Given that both local and distant recurrences were identified at 17, 30, and 34 months after ESD in our cases and in previous reports,\textsuperscript{18} yearly surveillance for 3 years with colonoscopy and/or CT might be acceptable if a rare but possible recurrence is a concern after ESD of huge intramucosal CRCs. However, additional data should be accumulated to suggest a reasonable surveillance strategy after endoscopic treatment of huge intramucosal CRCs.

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**Conflicts of Interest**

The authors have no financial conflicts of interest.