Case report

Two rare cases of node-positive differentiated gastric cancer despite their infiltration to sm1, their small size, and lack of lymphatic invasion into the submucosal layer

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Abstract

Early gastric cancer without lymph node metastasis has been reported after the analysis of many cases, and a consensus has been reached about this condition. We report two cases of node-positive differentiated sm1 gastric cancer without lymphatic invasion into the submucosal layer. Case 1 was a 73-year-old man who underwent EMR for 0-IIc early gastric cancer (EGC) on the gastric angle, with a histological diagnosis of tub1. Pathological examination revealed a 0-IIc lesion that was 12 mm in size and sm1 in invasion depth without lymphatic-vascular invasion. However, the infiltration in the submucosal layer was relatively wide. The patient subsequently underwent distal gastrectomy with D2 lymph node dissection. Pathological examination revealed level 2 lymph node metastasis. Case 2 was a 62-year-old woman who underwent ER for a 0-I+IIc-type EGC on the greater curvature of the antrum, with a histological diagnosis of tub1. Pathological examination revealed a 0-I+IIc-type lesion that was 15 mm in size and sm1 in depth. Lymphatic invasions in the muscularis mucosa were found, but none were seen in the submucosal layer. Two years later, follow-up computed tomography (CT) showed a lymph node swelling in the infrapyloric region. Distal gastrectomy with D2 dissection was then performed, and pathological examination revealed level 1 lymph node metastasis. Although the lesions in both patients satisfied the criteria of Gotoda et al. for minimal risk of nodal involvement, lymph node metastasis was observed in these patients. Curative surgery with lymph node dissection is thus required in patients with wide infiltration of the submucosal layer or lymphatic invasion in the muscularis mucosa.

Key words Gastric cancer · sm1 Infiltration depth · Lymph node metastasis

Introduction

Because lymph node metastasis is an important prognostic factor for patients with early gastric cancer (EGC), treatment strategy is determined according to the risk of nodal involvement. For patients with mucosal gastric cancer, much evidence has been reported supporting the idea that a limited subgroup of these patients is free from the risk of lymph node metastasis [1]. However, for patients with infiltration into the surface of the submucosal layer, the risk of metastasis has been uncertain. Recently, the risk of lymph node metastasis from EGC was analyzed in a large collaborative study sponsored by the National Cancer Center and our institute [2]. According to their data, none of 145 sm1 (cancer with submucosal invasion no more than 500 μm in depth) lesions were associated with lymphatic metastasis under the following conditions: lesions no more than 30 mm in size, differentiated histology, and lack of lymphatic or venous involvement. For the patients whose disease satisfied these conditions, it was considered permissible to apply endoscopic mucosal resection (EMR) and to omit lymph node dissection. In the two patients we report here, sm1 lesions were accompanied by lymph node metastasis, despite the lesions satisfying the strict conditions noted above. We report herein two rare cases of EGC that we encountered after completion of this collaborative study. All technical terms used in this report are in accordance with the Japanese classification of gastric carcinoma (second English edition) [3].

Report of cases

Case 1

Case 1 was a 73-year-old man who had received upper gastrointestinal endoscopy for stomach cancer screen-

ing at our center every 4 years, and no abnormalities had been pointed out until 2001. In August 2002, when he had still no gastric complaints, a depressed lesion (0-IIc) on the lesser curvature of the gastric angle was revealed by the examination (Fig. 1). A biopsy showed a well-differentiated tubular adenocarcinoma (tub1). The patient underwent EMR in September 2002. In this procedure, physiological saline was injected into the submucosal layer to elevate the lesion, which was treated by piecemeal resection and completely removed macro-

Fig. 1. Upper gastrointestinal endoscopy revealed a depressed lesion (0-IIc) on the lesser curvature of the gastric angle. A histological diagnosis of well-differentiated tubular adenocarcinoma (tub1) was made upon biopsy

Fig. 2. Pathological examination revealed that the early gastric cancer consisted of tubular adenocarcinoma (tub1) with penetration to the superficial submucosal layer. No components of poorly differentiated adenocarcinoma were found. The depth of submucosal invasion was about 200 μ m, but the invasion was about 1000 μ m in width. Lymphatic-vessel involvement was not found. H&E, scale bar 1000 μ m

scopically. The gross appearance of the tumor was 0-IIc-type EGC. Microscopically, it was a well-differentiated tubular adenocarcinoma (tub1) with sm1 infiltration, 12 mm in size, ly0, v0, INF β , VM(-), EB, but the lateral margin was uncertain because of the difficulty of reconstructing the pieces following the piecemeal resection. No components of poorly differentiated adenocarcinoma were found. Abdominal computed tomography (CT) did not reveal a swollen lymph node or liver metastasis. The tumor infiltration was limited to slight invasion of the submucosal layer. The depth of submucosal invasion was about 200 μ m, but the invasion was about 1000 μ m in width. Lymphatic-vessel involvement was not found (Fig. 2). Because the infiltration was spread over a relatively wide range and the lateral cut margin was unclear, pathologists recommended that the patient receive an additional surgical treatment. Accordingly, in November 2002, he underwent distal gastrectomy with D2 lymph node dissection. Histological examination of the resected specimen revealed no remnant cancer, but two positive lymph nodes were noted along the lesser curvature (no.3) and along the proximal part of the splenic artery (no.11p; 2/16), and this was diagnosed as level 2 lymph node metastasis. After an uneventful recovery, the patient was discharged from the hospital, and no cancer recurrence has been found 4.8 years after the gastrectomy.

Case 2

A 62-year-old woman had received upper gastrointestinal endoscopy for stomach cancer screening since 1997. In June 1999, a protruding lesion with an irregular

central depression, associated with conversion of the mucosal fold on the greater curvature of the antrum, was pointed out by the examination (Fig. 3). A biopsy revealed a well-differentiated tubular adenocarcinoma (tub1). She underwent ER in June 1999. The tumor was removed in one piece, and the gross appearance was 0-I+IIc-type EGC. The tumor consisted of a well-

Fig. 3. Upper gastrointestinal endoscopy revealed a protruding tumor with an irregular central depression on the greater curvature of the antrum. A histological diagnosis of well-differentiated tubular adenocarcinoma (tub1) was made upon biopsy. Endoscopic resection was done by one-piece resection

differentiated tubular adenocarcinoma (tub1), 15 mm in size, ly0, v0, INF β , VM(-), LM(-), EB, showing sm1 infiltration. No components of poorly differentiated adenocarcinoma were found. The tumor, which infiltrated the surface of the submucosal layer (about 100 μ m), had also a few lymphatic invasions in the muscularis mucosa, but no lymphatic invasion was found in the submucosal layer (Fig. 4).

The patient was followed up carefully, and 2 years later an abdominal CT revealed lymph node swelling in the infrapyloric region (no. 6), which was diagnosed as lymph node metastasis. We then recommended a surgical operation, and she underwent distal gastrectomy with D2 lymph node dissection in July 2001. Histological examination of the resected specimen revealed no remnant cancer around the ER-treated scar, but three positive lymph nodes were found in the infrapyloric region (no.6; 3/26). A diagnosis of level 1 lymph node metastasis was confirmed. After an uneventful recovery, she was discharged from the hospital and has had no recurrence 5 years after the gastrectomy.

Discussion

Endoscopic resection (ER) has been accepted as curative resection for early gastric cancer (EGC) without lymph node metastasis for a long time since its introduction. It is well known that lesions satisfying the following criteria are free of the risk of lymph node metastasis: intramucosal differentiated tumor; elevated lesion less than 30 mm in size, or depressed lesion less than 10 mm; and lesions without an ulcer or ulcer scar. Recently,

Fig. 4. Pathological examination revealed that the early gastric cancer consisted of tubular adenocarcinoma (tub1) with minute penetration to the superficial submucosal layer. The depth of submucosal infiltration was within 100 μ m, and a few lymphatic invasions were revealed in the muscularis mucosa. No lymphatic invasion was found in the submucosal layer. No components of poorly differentiated adenocarcinoma were found. H&E, scale bar 3000 μ m

the development of endoscopic submucosal dissection (ESD) using an insulated-tip knife has made it possible for us to resect larger lesions, even those more than 30 mm in diameter, in differentiated tumors confined to the mucosal layer. As the indications for ESD are being widened, treatment indications for EGC with minute submucosal invasion have become the subject of debate. The degree of submucosal invasion is recognized as the most significant risk factor correlating with nodal involvement, while lymphatic invasion and histologic differentiation are also important risk factors for nodal involvement [4, 5]. On the other hand, several reports have demonstrated the safety from lymphatic metastasis in a limited subgroup of sm1 gastric cancers [6–11]. This has raised the question of whether distal or total gastrectomy with lymph node dissection [12–14] is necessary for small, differentiated gastric cancers with a depth of sm1.

Recently Gotoda et al. [2] reported the incidence of lymph node metastasis after investigating 5265 EGCs at the National Cancer Center in Japan and our institute. They demonstrated the safety of endoscopic treatment for cancers with infiltration to the superficial submucosal layer. Among 1230 differentiated intramucosal tumors, lesions measuring less than 30 mm in size were not associated with lymph node metastasis, despite the presence or absence of scar ulcer, and those without ulceration did not show nodal involvement despite their size. In addition, none of 145 differentiated cancers less than 30 mm in diameter without lymphatic-vascular involvement were associated with lymph node metastasis to the extent that the penetration was limited to within 500 μ m into the submucosal layer (sm1). In Japan, this study of Gotoda et al. [2] has been used frequently in decision-making for additional surgical treatment following pathological examinations after ESD, and the data have been used as baseline in the development of gastric cancer treatment guidelines as well.

The width of infiltration in the submucosal layer and lymphatic involvement in the mucosal layer have not been described in detail in earlier reports, but Ishigami et al. [15] demonstrated a significant correlation between lymphatic invasion and the degree of submucosal invasion, not only regarding the depth of invasion but also with the width of tumor infiltration. Listrom et al. [16] have provided a detailed description of the anatomical distribution of gastric lymphatics, and have shown that lymphatic vessels are also found in the lower third of the lamina propria or muscularis mucosa. Concerning lymphatic-vascular involvement, pathological reports commonly mention the status below the mucosal layer. In the report of Gotoda et al. [2], which was the collaborative study sponsored by the National Cancer Center and our institute, lymphatic-vascular permeation was also evaluated within the submucosal layer, but not in

the lamina propria, and this permeation within the submucosal layer had been confirmed by a pathologist at our institute.

In the present study, both patients were treated with EMR, as according to the criteria of Gotoda et al. [2], their lesions were associated with a minimal risk of lymph node metastasis. In case 1, evaluation of the lateral margin was difficult because of the piecemeal resection. Precise pathological evaluation, carried out at 2-mm intervals, showed an sm1 lesion 12 mm in diameter, without vessel permeation in the submucosal layer; however, it cannot be denied that we might have overlooked the presence of lymphatic invasion in the layer because of a “burning” effect on the resection margin following the piecemeal resection. In case 2, the lesion, treated with en-bloc resection, was 15 mm in size, in which lymphatic invasion was observed in the lamina propria, but not in the submucosal layer. It is considered that evaluation of the differentiation type at the deepest invasive site of a carcinoma is essential. In the present study, neither patient had any poorly differentiated adenocarcinoma components; the lesions consisted only of well-differentiated components.

In 2000, following the publication of the report of Gotoda et al. [2], we carried out a study in which we examined details of 70 sm1 well-differentiated gastric cancers in 2355 patients who had undergone EMR at our hospital. Of these 70 sm1 cases, lymphatic-vascular invasion was observed in 13 cases, and it was not found in 57 cases. Lymph node metastasis was present in 3 of the 57 cases without lymphatic-vascular invasion (5.3%); 2 of these cases have been presented here—in the other case, the lesion was 63 mm in size. Nodal involvement was present in 4 of the 13 cases with lymphatic-vascular invasion (31%). Among sm1 cancers no more than 30 mm in size showing differentiated histology, only the 2 cases presented here showed lymph node metastasis. Therefore, the 2 cases presented here were considered to be extremely rare.

Given that these cases are rare but existing, we should not determine the risk of lymph node metastasis in cases of sm1 gastric cancer based only upon the lesion size or extent of lymphatic involvement in the submucosal layer or upon the degree of tumor differentiation. More careful evaluation should be carried out, investigating additional characteristics such as the width of submucosal invasion or the extent of lymphatic involvement in the mucosal layer.

From these clinical observations, it is too early to endorse the complete applicability of ER in all cases of sm1 gastric cancer. Careful follow-up with the use of annual abdominal CT scans is required for all types of sm1 gastric cancer for the early detection of lymph node metastasis. When lymph node metastasis is suspected, additional surgical treatment should be required.

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Editorial comment

A word of caution regarding easy expansion of the indications for endoscopic submucosal dissection in early gastric cancer

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With recent improvements in resection technique using the insulated-tip (IT) knife, hook knife, and flex knife, the number of endoscopic submucosal dissections (ESDs) and the proportion of one-piece resections have dramatically increased and the local recurrence rate has decreased. Consequently, there are moves to expand the indications for ESD, according to the article by T. Gotoda et al. [1]. However, both pathologists and clinicians should be prudent in deciding that additional surgery is not necessary.

In this issue of the journal, H. Nagano et al. [2] reported two rare cases in which unexpected lymph node metastases were found by additional surgery after ESD. In the past, as mentioned in this article, pathologists did not usually check for lymphatic invasion in the mucosal layer or in the muscularis mucosae, but in fact, a few patients showing such involvement had lymph

node metastases. At the National Cancer Center Hospital, Tokyo, we had a patient with lymphatic invasion in the muscularis mucosae which, by deeper-cut examination, was found to connect to submucosal lymphatic invasion. Lymph node metastasis was discovered in this patient. In another patient with 20-mm IIa without lymphatic invasion, submucosal invasion within 500 µm (sm1 invasion) was discovered, and he too had lymph node metastasis. Histologically, the invaded portion in the submucosal layer was of the poorly differentiated type in a small area. Based on the report by Gotoda et al., such a patient could be followed up without additional surgery. However, these patients actually had nodal metastasis. Some authors have reported that lesions with wide submucosal invasion showed a greater tendency to have nodal metastasis. The correlation between the width and depth of submucosal invasion and their relationship with nodal metastasis should be further studied, as in colon cancer.

With regard to endoscopically resected material, pathologists should carefully examine the mucosal layer and the muscularis mucosae to exclude lymphatic invasion. If there is submucosal invasion, even minute, the histological grade should be precisely determined, and if it includes even a small portion of poorly differentiated histology, additional surgery should be considered.

Otherwise, detailed informed consent, with explanation of the risk of nodal metastasis, and careful observation including CT scan are mandatory.

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