Clinical Case Report

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Risk of multiple early gastric cancers in a patient with precursor lesions and endoscopic surveillance for 7 years

A case report

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Abstract

Rationale: Severe mucosal atrophy or intestinal metaplasia is a risk factor for synchronous and metachronous intestinal gastric cancer. Magnifying endoscopy with narrow-band imaging was useful for assessing differentiated early gastric cancer (EGC).

Patient concerns: A 62-year-old Chinese female was diagnosed with 5 multiple EGCs or high-grade dysplasia (HGD) with endoscopic surveillance for 7 years.

Diagnoses: Synchronous and metachronous multiple EGCs.

Interventions: Endoscopic submucosal dissection (ESD) with en bloc resection was performed for all 5 multiple lesions. The ESD specimens were pathologically diagnosed with adenocarcinoma confined to the mucosa or HGD.

Outcomes: After endoscopy resection, no residual, recurrent, or synchronous lesions were detected by endoscopic surveillance after ESD.

Lessons: Long-term, meticulous endoscopic surveillance is needed to monitor risk factors associated with multiple EGCs in patients with severe mucosal atrophy or intestinal metaplasia despite successful *Helicobacter pylori* eradication.

Abbreviations: EGC = early gastric cancer, ESD = endoscopic submucosal dissection, HGD = high-grade dysplasia, LGD = low-grade dysplasia, ME-NBI = magnifying endoscopy with narrow-band imaging.

Keywords: dysplasia, endoscopic submucosal dissection, *Helicobacter pylori*, magnifying endoscopy with narrow-band imaging, multiple early gastric cancers

1. Introduction

The ability to detect multiple early gastric neoplasms has increased in recent years owing to advances in endoscopic diagnostic techniques and pathologic examinations. Endoscopic submucosal dissection (ESD) with en bloc resection is useful for treating early gastric cancer (EGC) or high-grade dysplasia (HGD). However, the development of synchronous or metachronous multiple EGCs in the remnant stomach after ESD remains a major clinical problem.[1] Therefore, oncologists should be highly suspicious of the presence of multiple EGCs or premalignant lesions in high-risk patients.

According to the Japanese Gastric Cancer Association criteria, tumors can be macroscopic and are classified into the following 3 types: elevated (types 0–I, 0–IIa, 0–I + IIa, 0–IIa + IIb, 0–IIa +IIc); flat (type 0–IIb); and depressed (types 0–IIc, 0–III, 0–IIc + IIa, and 0–III + IIa).[2] Differentiated gastric cancer can be classified histologically as papillary adenocarcinoma or well and moderately differentiated tubular adenocarcinoma. Magnifying endoscopy with narrow-band imaging (ME-NBI), the use of which is steadily increasing, is useful for assessing the lateral spread and histological type of differentiated EGC and for enabling targeted biopsies.[3–5]

Here, we report a patient with multiple EGCs who underwent ESD of synchronous and metachronous tumors, an upgraded diagnosis from an original diagnosis of low-grade dysplasia (LGD), after 7 years of endoscopic surveillance.

2. Methods

Ethical approval was not necessary for this case report. Informed written consent was obtained from the patient for publication of this case report and the accompanying images.

3. Case report

We describe a 62-year-old Chinese female who was diagnosed with multiple EGCs with successful eradication of *Helicobacter pylori* in December 2017. The first lesion located in the greater

Editor: N/A.

This work was supported by the National Key R&D Program of China (2016YFC1303601).

The authors have no funding and conflicts of interest to disclose.

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Medicine (2019) 98:22(e15686)

Received: 7 December 2018 / Received in final form: 11 April 2019 / Accepted: 22 April 2019

http://dx.doi.org/10.1097/MD.0000000000015686

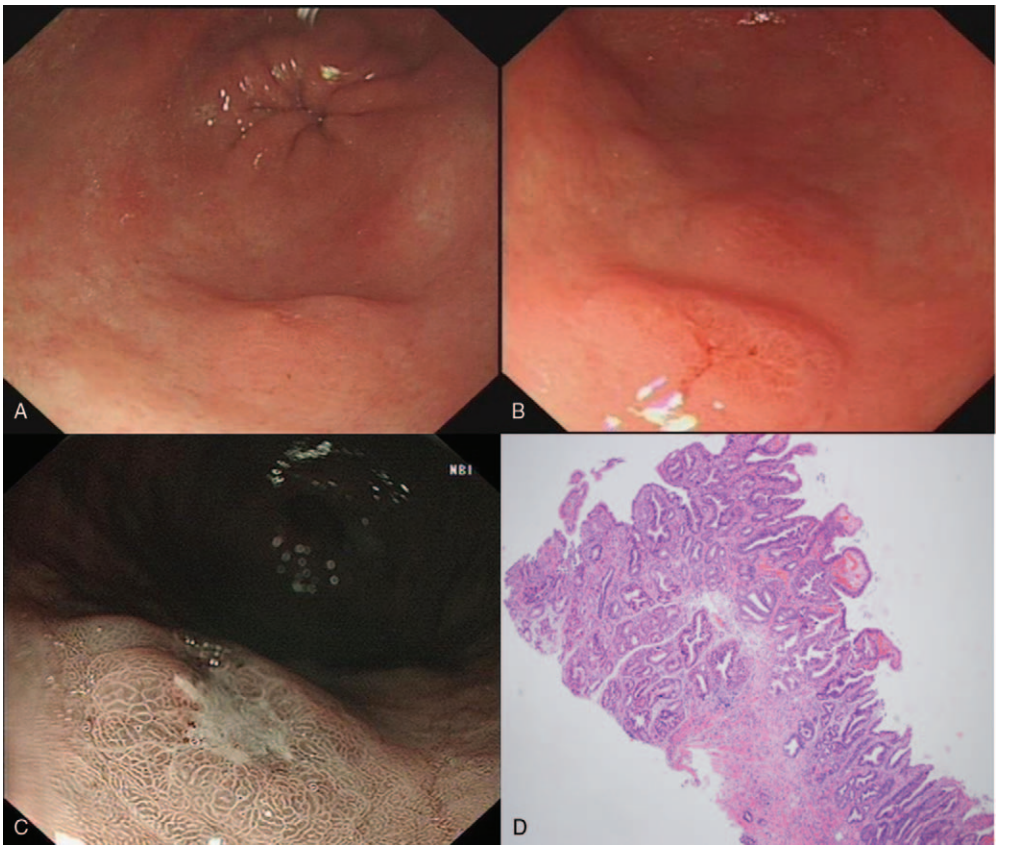

Figure 1. Endoscopy showed a small elevated and lightly depressed lesion (IIa + IIc, 1.5 cm × 1.0 cm) at antrum greater curvature side. (A–C) Endoscopy surveillance in July 2010, March 2014, and July 2016, respectively. (D) Histology of endoscopic forceps biopsy showed low-grade dysplasia with moderate-to-severe atrophy and intestinal metaplasia.

curvature of the antrum was detected at the patient's first endoscopy in July 2010. It was classified as type IIa + IIc with dimensions of 1.5×1.0 cm. It had a nodular surface with a central depression and redness (Fig. 1). The patient was diagnosed with *H pylori* infection based on a rapid urea enzyme test and eradication therapy was performed (esomeprazole, amoxicillin, clarithromycin, and bismuth quadruple therapy). Two synchronous early gastric lesions were also detected during the first endoscopy. One of these lesions was located on the lesser curvature of the antrum. It was classified as type IIa + IIc with dimensions of 1.0×1.0 cm. It also had a nodular surface with a central depression and redness (Fig. 2). The other lesion was located at the lesser curvature of lower gastric corpus. It was classified as type IIb with dimensions of 2.0×1.0 cm. It had a nodular appearance and a faded mucosa (Fig. 3). Over the next 7 years, she underwent endoscopy 4 times (August 2011, November 2012, March 2014, and July 2016). The 3 lesions did not show invasive features under white light endoscopy and the pathological diagnosis of endoscopic biopsies was LGD with moderate-to-severe atrophy and intestinal metaplasia (Figs. 1–3).

In August 2017, at her sixth endoscopy, 2 new small emerging lesions were observed. Both lesions had a central depression, surface redness, or a nodular surface under white light endoscopy, which are risk factors for EGC. ME-NBI revealed irregular microvascular and microsurface patterns with a demarcation line and confirmed the presence of the 3 lesions previously detected. The lesions were highly suspected of being EGCs according to the VS classification system reported by Yao et al.[6] The fourth lesion was located on the greater curvature of the antrum close to the corpus. It was classified as type IIc, with dimensions of 0.6×0.5 cm. It had a central depression and redness (Fig. 4). The fifth lesion was located on the posterior wall of the gastric angulus. It was classified as type I with dimensions of 0.5×0.5 cm. It had an elevated, nodular surface (Fig. 5).

In December 2017, she was admitted to our hospital for endoscopic resection of the lesions. Contrast-enhanced computed tomography did not show any lymphadenopathy before ESD. ESD with en bloc resection was performed for all 5 lesions. Resection margins were negative and there were no signs of lymphovascular invasion. Using the ESD tissue specimens, the first 4 lesions were pathologically diagnosed as adenocarcinoma confined to the mucosa whereas the fifth lesion was diagnosed as HGD according to the Japanese Classification of Gastric Carcinoma[2] (Figs. 4–8).

After endoscopic treatment, she has been followed up with gastroscopic examination. She is alive in a good clinical condition. Endoscopic surveillance has revealed no further abnormalities, with no evidence of residual, recurrent, or synchronous lesions at 3, 6, and 12 months after ESD.

4. Discussion

Owing to the ongoing development of endoscopic diagnostic techniques, the detection rate of multiple EGCs has increased

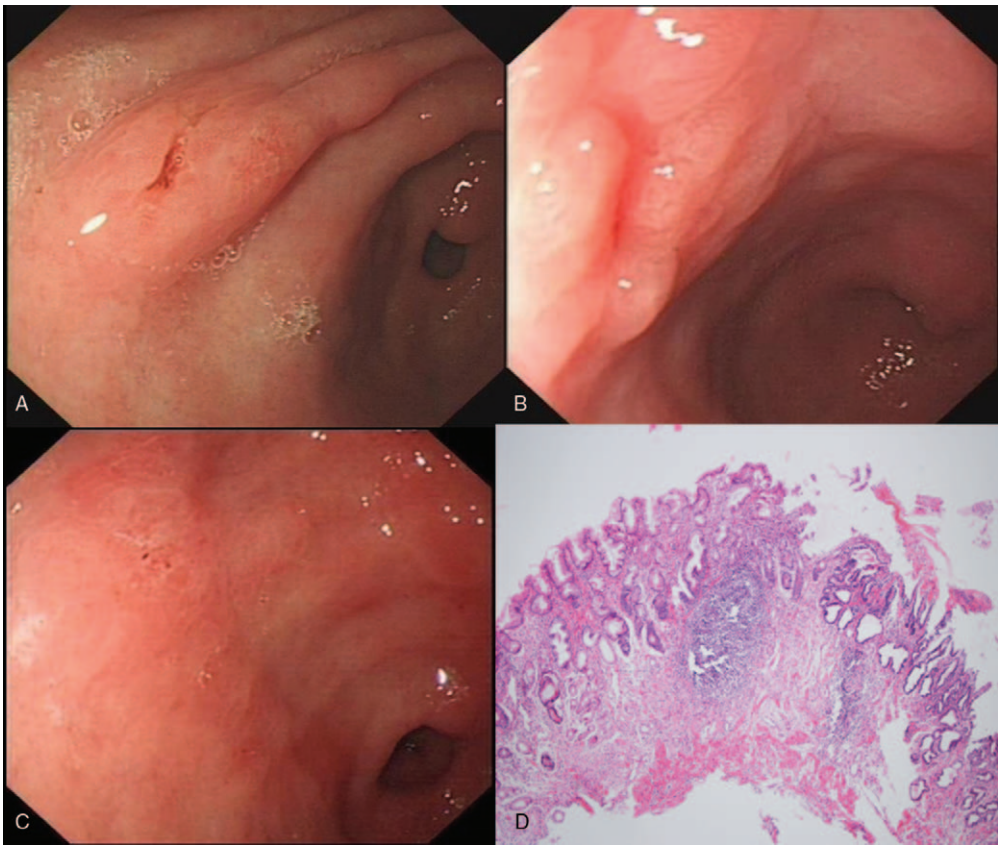

Figure 2. Endoscopy showed a small elevated and lightly depressed lesion (IIa + IIc, 1.0 cm × 1.0 cm) at antrum lesser curvature side. (A–C) Endoscopy surveillance in July 2010, November 2012, and July 2016, respectively. (D) Histology of endoscopic forceps biopsy showed low-grade dysplasia with moderate-to-severe atrophy and intestinal metaplasia.

significantly in recent years. According to the diagnostic criteria proposed by Moertel et al,[7] synchronous cancers are lesions diagnosed with an interval of less than 12 months, whereas metachronous cancers are detected at an interval exceeding 12 months. Moertel et al[7] defined multiple gastric cancers as follows: each lesion must be pathologically proven to be malignant; each lesion must be distinctly separated from other lesions by a microscopically normal gastric wall; and the lesions must not represent a metastatic tumor or a local extension. Based on this definition, this case was diagnosed with synchronous and metachronous multiple EGCs based on the initial detection of 3 lesions in July 2010, followed by another 2 lesions in August 2017.

To reduce the possibility of missing the diagnosis of multiple gastric cancers, it is important to identify the main risk factors for multiple EGCs. Previous studies[1,8,9] revealed that older age (over 60 years) and differentiated histological type are risk factors for synchronous or metachronous multiple gastric neoplasms. In our case, the pathological diagnosis of the first 3 lesions was LGD with moderate-to-severe atrophy and intestinal metaplasia. According to the Correa hypothesis,[10] intestinal gastric cancer develops from precursor lesions, such as atrophic gastritis, intestinal metaplasia, and adenomas (LGD/HGD). We conclude that pathological diagnoses of severe atrophy and metaplasia are risk factors for synchronous and metachronous gastric neoplasms. The majority of gastric cancers develop in elderly patients with a history of intestinal metaplasia, and many of these patients develop multiple gastric lesions.[11] This case had multiple EGCs with differing histological features, including elevated, depressed, or flat features. These findings are inconsistent with those of previous studies reporting risk factors for multiple EGCs.[12,13] We hypothesize that intestinal EGC may undergo multiple histologic stages before submucosal invasion.

The natural course of dysplastic gastric lesions is unclear; in western countries, the rate of progression from dysplasia to gastric cancer ranged from 0.6% to 6% per year according to the grade of dysplasia.[14] The discrepancy in diagnosis between endoscopic forceps biopsy and ESD specimens is another clinical concern, with discrepancy rates ranging from 20% to 76%.[15] In our patient, 3 lesions were pathologically diagnosed as LGD by endoscopic biopsies and were monitored for 7 years by endoscopy. The diagnosis was subsequently upgraded to adenocarcinoma confined to the mucosa based on the ESD specimens. For gastric epithelial neoplasia before ESD, the diagnostic rate using a single endoscopic forceps biopsy was 65.7% to 70.8% and the LGD diagnosis was upgraded to EGC in 6.0% of cases.[16] There are a few possible reasons for the discrepancies in diagnosis between endoscopic forceps biopsy and ESD.[17] First, biopsy specimens are too small to detect the exact core of adenocarcinoma lesions. Second, cancerous lesions may exist focally within a background of dysplastic lesions. In prior studies, a central depression, a nodular surface, surface redness, and lesions with a maximum diameter of >10 mm were risk factors for EGC in patients undergoing ESD of LGD.[15,17–19] To decrease the diagnostic discrepancy between endoscopic

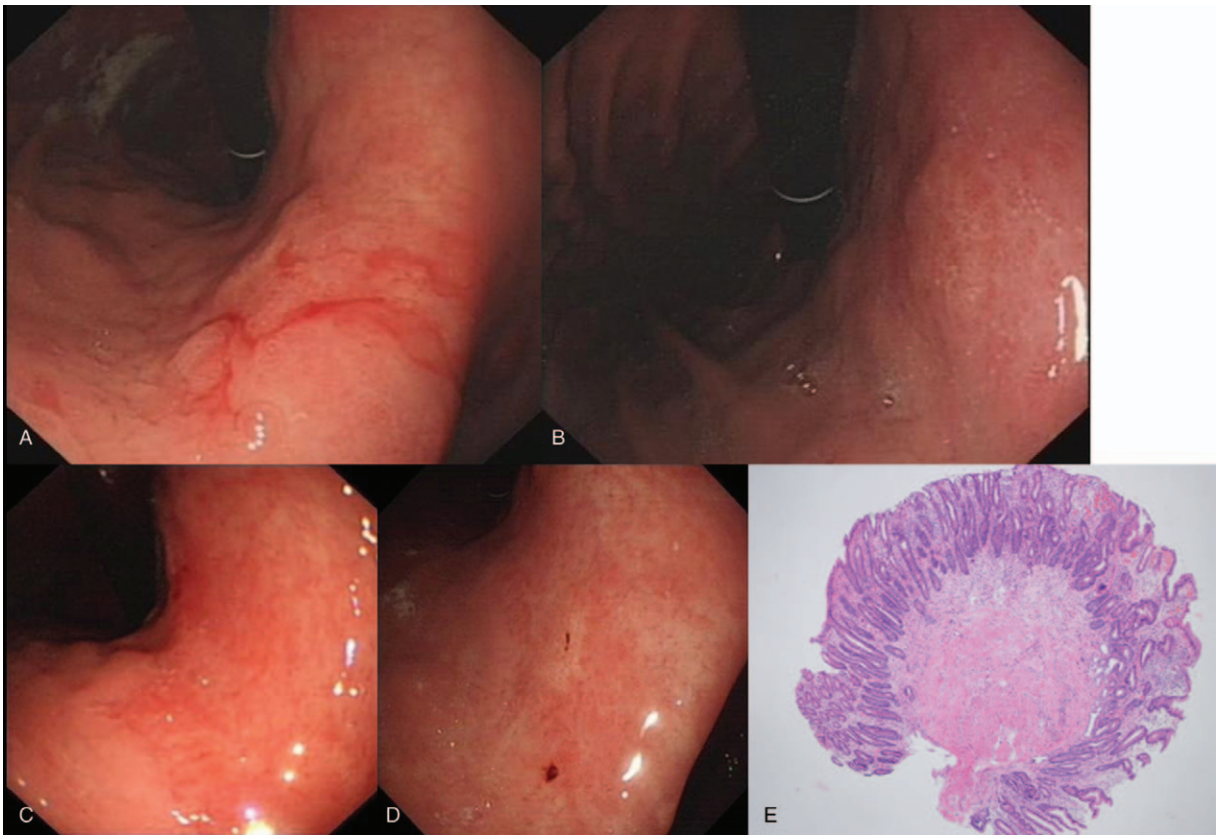

Figure 3. Endoscopy showed a flat lesion (IIb, 2.0 cm × 1.0 cm) at lesser curvature of lower gastric corpus. (A–D) endoscopy surveillance in July 2010, November 2012, March 2014, and July 2016, respectively. (E) Histology of endoscopic forceps biopsy showed low-grade dysplasia with moderate-to-severe atrophy and intestinal metaplasia.

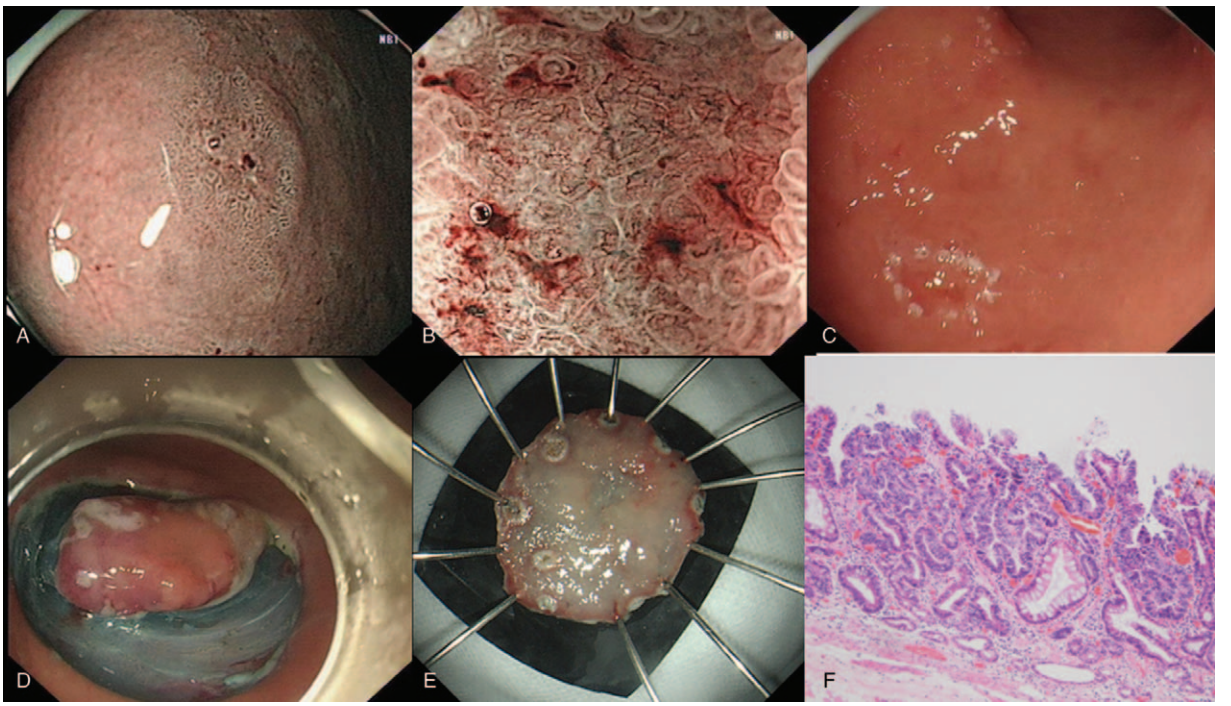

Figure 4. The fourth lesion without a biopsy before ESD. (A) Endoscopy with NBI showed the lesion at antrum greater curvature side near corpus with superficial depressed (IIc, 0.6 cm × 0.5 cm). (B) ME-NBI showed irregular MVP and MSP with a DL. (C, D) Endoscopic finding during the ESD. (E) En bloc-resected ESD specimen. (F) Pathologically diagnosed with adenocarcinoma confined to mucosa. DL = demarcation line, EGC = early gastric cancer, ESD = endoscopic submucosal dissection, ME-NBI = magnifying endoscopy with narrow-band imaging, MSP = microsurface pattern, MVP = microvascular pattern.

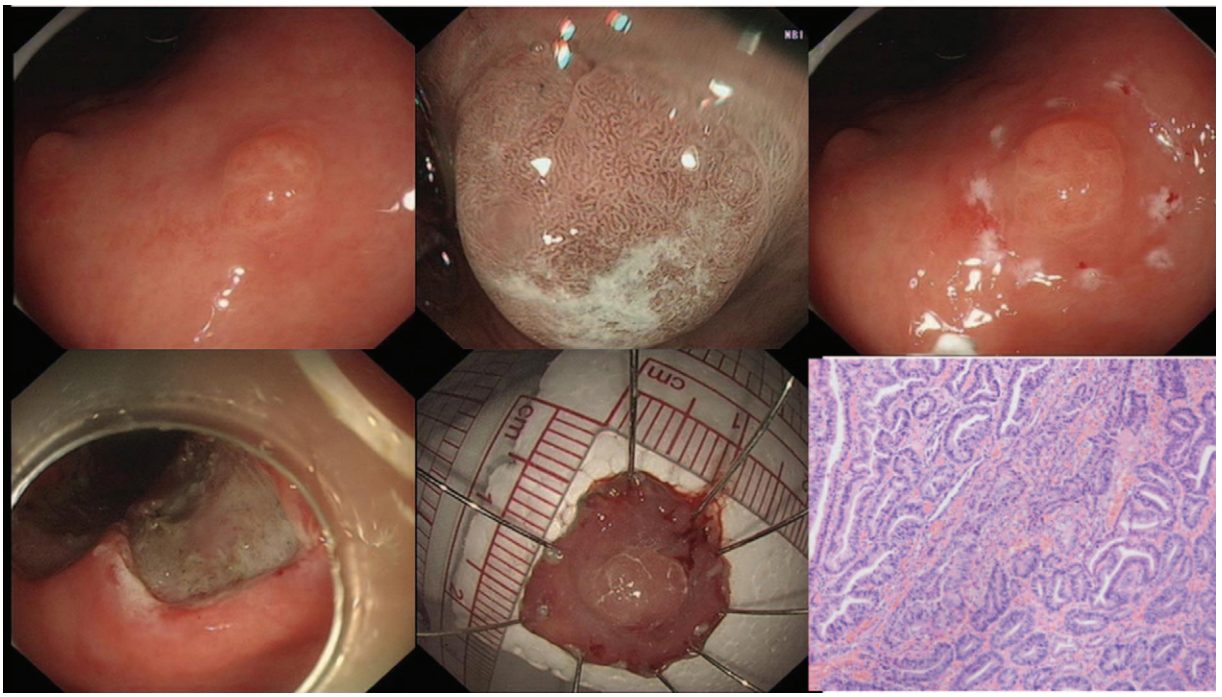

Figure 5. The fifth lesion without a biopsy before ESD. (A) Conventional endoscopic image: the lesion located at gastric angulus posterior wall (I, 0.5 cm × 0.5 cm). (B) ME-NBI showed irregular MVP and MSP with a DL. (C, D) Endoscopic finding during the ESD. (E) En bloc-resected ESD specimen. (F) Pathologically diagnosed with high-grade dysplasia. DL = demarcation line, ESD = endoscopic submucosal dissection, ME-NBI = magnifying endoscopy with narrow-band imaging, MSP = microsurface pattern, MVP = microvascular pattern.

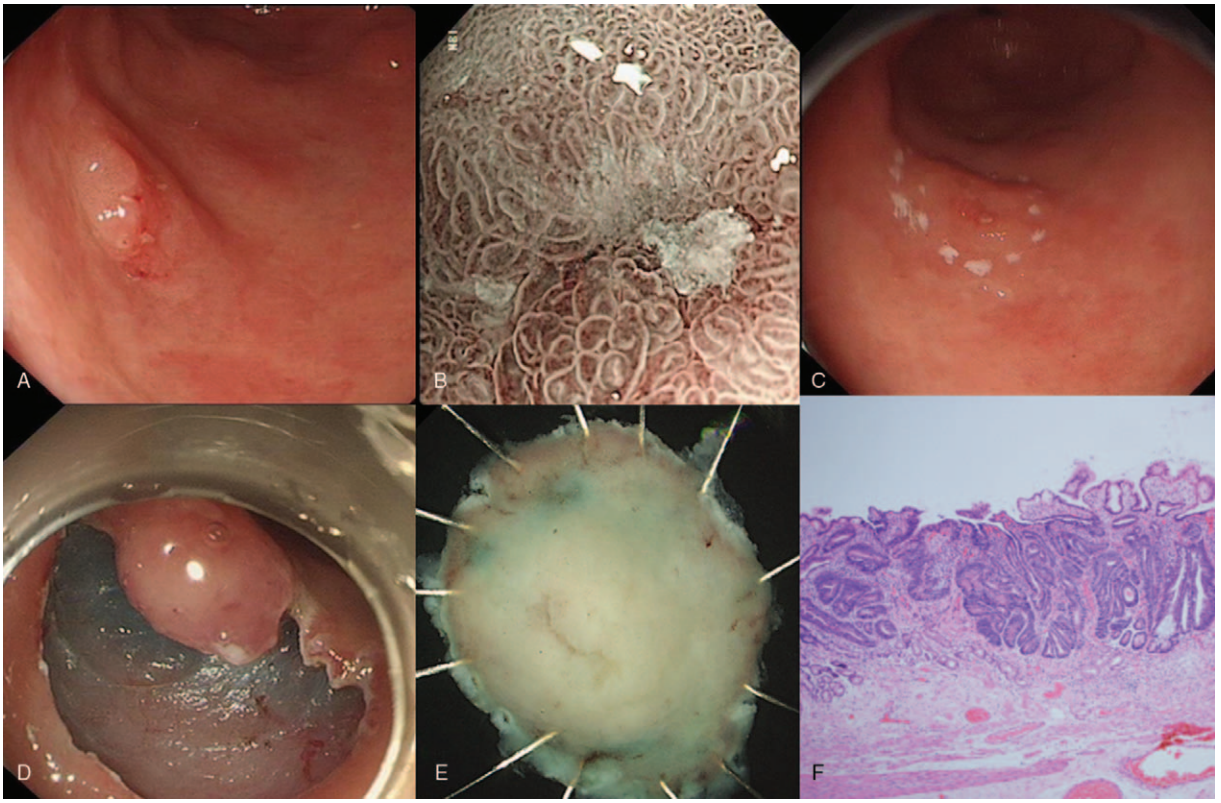

Figure 6. The first lesion upgraded diagnosis from low-grade dysplasia to EGC. (A) Conventional endoscopic image: the lesion located at antrum greater curvature side with nodular surface, central depression, and redness. (B) ME-NBI showed irregular MVP and MSP with a DL. (C, D) Endoscopic finding during the ESD. (E) En bloc-resected ESD specimen. (F) Pathologically diagnosed with adenocarcinoma confined to mucosa. DL = demarcation line, EGC = early gastric cancer, ESD = endoscopic submucosal dissection, ME-NBI = magnifying endoscopy with narrow-band imaging, MSP = microsurface pattern, MVP = microvascular pattern.

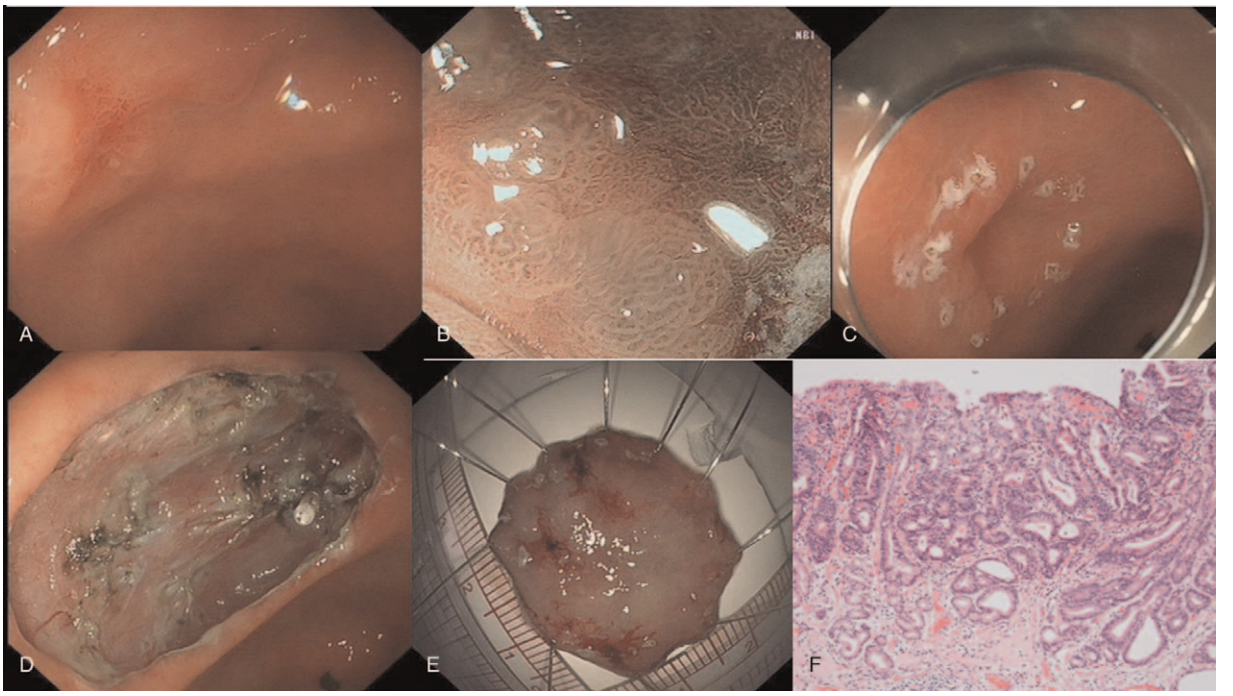

Figure 7. The second lesion upgraded diagnosis from low-grade dysplasia to EGC. (A) Conventional endoscopic image: the lesion located at antrum lesser curvature side with central depression and redness. (B) ME-NBI showed irregular MVP and MSP with a DL. (C, D) Endoscopic finding during the ESD. (E) En bloc-resected ESD specimen. (F) Pathologically diagnosed with adenocarcinoma confined to mucosa. DL = demarcation line, EGC = early gastric cancer, ESD = endoscopic submucosal dissection, ME-NBI = magnifying endoscopy with narrow-band imaging, MSP = microsurface pattern, MVP = microvascular pattern.

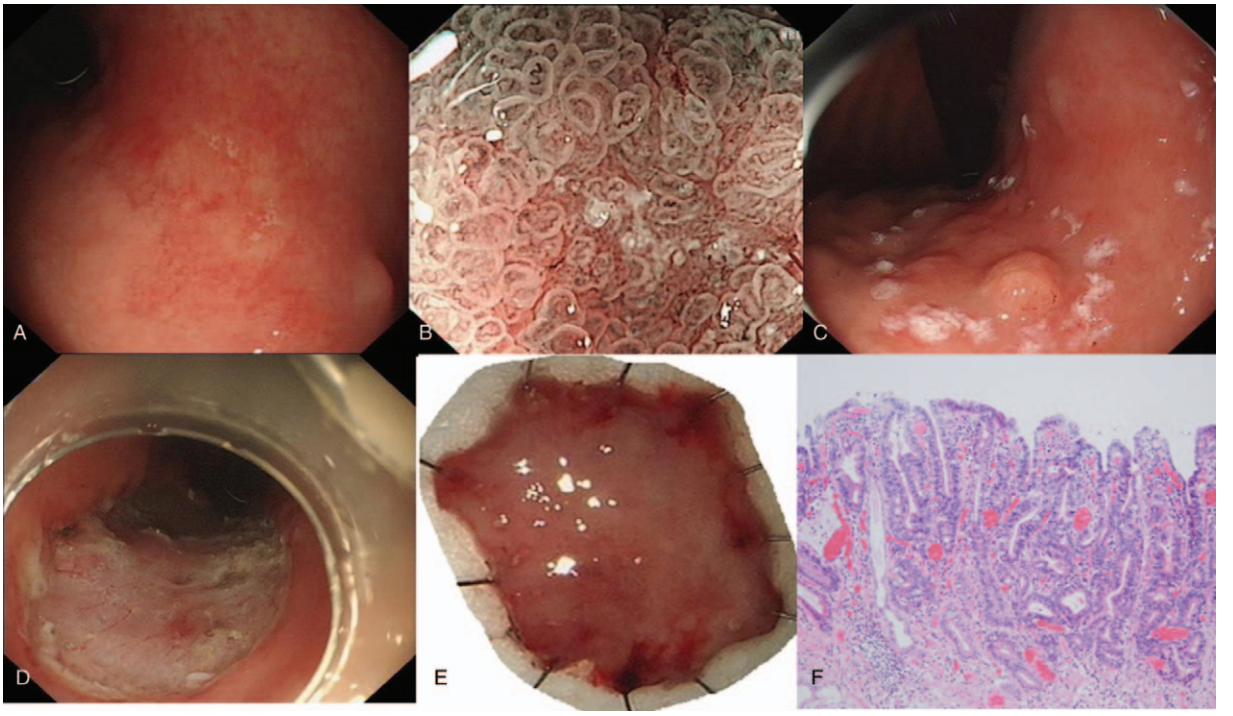

Figure 8. The third lesion upgraded diagnosis from low-grade dysplasia to EGC. (A) Conventional endoscopic image: the lesion located at lesser curvature of lower gastric corpus with nodular and white faded surface. (B) ME-NBI showed irregular MVP and MSP with a DL. (C, D) Endoscopic finding during the ESD. (E) En bloc-resected ESD specimen. (F) Pathologically diagnosed with adenocarcinoma confined to mucosa. DL = demarcation line, EGC = early gastric cancer, ESD = endoscopic submucosal dissection, ME-NBI = magnifying endoscopy with narrow-band imaging, MSP = microsurface pattern, MVP = microvascular pattern.

forceps biopsy and resected specimens, it is helpful to identify possible risk factors for EGC in patients with LGD and perform a targeted biopsy of suspected EGC under ME-NBI.[5,20,21] Based on our experience in this case, we suggest that endoscopic resection should be seriously considered in patients with gastric LGD considered indefinite based on endoscopic forceps biopsy if any risk factors for EGC are observed by endoscopy.

ME-NBI can provide a very accurate diagnosis of differentiated EGCs by acquiring detailed information about the microvascular and microsurface patterns with a demarcation line.[6,22–24] ME-NBI is conventionally used for the diagnosis of suspected EGC lesions. According to the VS classification system described by Yao et al,[6] ME-NBI can be used to establish a diagnosis of EGC in cases with irregular microvascular or microsurface patterns with a demarcation line.

H pylori infection is closely related to the occurrence of atrophic gastritis, intestinal metaplasia, and subsequent gastric neoplasms. The beneficial effects of *H pylori* eradication may be weakened by severe tissue atrophy and intestinal metaplasia. The degree of intestinal metaplasia in the surrounding mucosa was reported to be a significant risk factor for synchronous multiple gastric cancers.[9] However, there is some controversy regarding the effect of *H pylori* eradication on the occurrence of metachronous gastric cancer.[25,26] In our patient, metachronous gastric cancers were detected 7 years after *H pylori* eradication. Therefore, we assume that severe mucosal atrophy or intestinal metaplasia, but not *H pylori* infection status, was an independent risk factor for metachronous EGC.[27] Consistent with the previous studies,[28–32] our case suggests that patients with synchronous multiple neoplasms are at high risk of developing metachronous multiple neoplasms regardless of *H pylori* infection status. Therefore, meticulous, long-term endoscopic surveillance is necessary for patients with multiple gastric cancers and severe mucosal atrophy or intestinal metaplasia, even after successful *H pylori* eradication.

Endoscopic resection is widely accepted as a standard treatment for early gastric neoplasms. Endoscopic resection can preserve the entire stomach but patients may develop synchronous or metachronous multiple lesions in the remnant gastric mucosa. Thus, establishing an optimal surveillance strategy is important for detecting multiple lesions during the early stages of disease, but the optimal surveillance schedule for detecting multiple lesions remains unclear. Some authors reported that the increased risk of metachronous cancers did not persist for more than 10 years of surveillance.[29,33–35] Based on these studies, and to detect synchronous cancers that might have been missed in initial endoscopy, we suggest follow-up intervals of 3months, 6 months, and 1 year after ESD, and then annually for 5 to 10 years after initial ESD.

In conclusion, based on our experience with this case and a review of the literature, we suggest the following. First, severe mucosal atrophy and intestinal metaplasia are risk factors for synchronous and metachronous multiple gastric neoplasms. Second, *H pylori* eradication may not diminish the risk of metachronous multiple gastric neoplasms in patients with severe mucosal atrophy or intestinal metaplasia. Third, due to the discrepancy associated with conventional endoscopy biopsy, any cases of LGD with a central depression, a nodular surface, or surface redness are at high risk of EGC and endoscopic resection should be considered. Fourth, ME-NBI is useful for the diagnosis of EGC and enabling targeted biopsies. Finally, meticulous, long-term endoscopic surveillance is needed to help detect multiple gastric cancers in patients with severe mucosal atrophy or intestinal metaplasia.

Author contributions

Data curation: Hui Pan.
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Supervision: Lanzai Liu, Chao Wang, Jiansu Chen.
Visualization: Houqiang Li.
Writing – original draft: Hui Pan.
Writing – review & editing: Chaoying Fang.

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