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【 CASE REPORT 】

Synchronous Early Gastric Cancer/Neuroendocrine Tumor Associated with Autoimmune Gastritis Completely Resected with Endoscopic Submucosal Dissection

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Abstract:
Synchronous early gastric cancer/neuroendocrine tumor (NET) associated with autoimmune gastritis is rare, and its endoscopic and pathological features remain poorly described. Screening esophagogastroduodenoscopy performed on a 71-year-old man revealed a whitish, superficial elevated lesion and a submucosal tumor with redness that appeared slightly centrally depressed. Endoscopic submucosal dissection (ESD) allowed these lesions to be resected with negative margins, and they were diagnosed as tubular adenocarcinoma, well-differentiated type (tub1), pT1a (M) and NET G1, pT1b (SM). To our knowledge, this is the first report describing the endoscopic and pathological findings of synchronous early gastric cancer/NET that was amenable to complete resection with ESD.

Key words: gastric carcinoma, gastric NET, endoscopic treatment

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Introduction

In the 2010 WHO classification, gastrointestinal neuroendocrine tumors (NETs) are classified into NET G1, G2, and neuroendocrine carcinomas (NECs) according to the grade of malignancy of each component (1). While autoimmune gastritis is associated with two types of gastric neoplasms, i.e. gastric cancer and NET (2), synchronous gastric cancer/NET associated with autoimmune gastritis is rare, and its endoscopic and pathological features remain poorly described.

We herein report a case of synchronous early gastric cancer/NET in a patient with autoimmune gastritis that was amenable to complete resection with endoscopic submucosal dissection (ESD).

Case Report

Screening esophagogastroduodenoscopy (EGD) performed on a 71-year-old man revealed a whitish, superficial elevated lesion and a submucosal tumor with redness that appeared slightly centrally depressed in the posterior wall of the gastric angle on white-light imaging (WLI) (Fig. 1A and B). On narrow-band imaging (NBI), the lesion was depicted as a whitish, well-circumscribed superficial lesion (Fig. 1C). Furthermore, an irregular microvascular pattern was shown to be present within the demarcation line on magnifying NBI (Fig. 1D). Based on these findings, the lesion was diagnosed as early gastric cancer.

An EGD biopsy revealed adenoma and endocrine cell micronests (ECMs). Laboratory data showed the patient to be positive for anti-parietal cells, anti-intrinsic factor antibodies, and hypergastrinemia (gastrin, up to 1,440 pg/mL) but negative for serum *Helicobacter pylori* IgG antibody (<3 U/mL). In addition, an examination of the biopsy specimen revealed proximal-predominant gastric mucosal atrophy and scattered ECM in the proximal region (Fig. 2) with no evidence of *H. pylori* colonization, suggesting the presence of autoimmune gastritis.

ESD was performed on the suspected well-differentiated tubular adenocarcinoma/ NET for a biopsy and endoscopic

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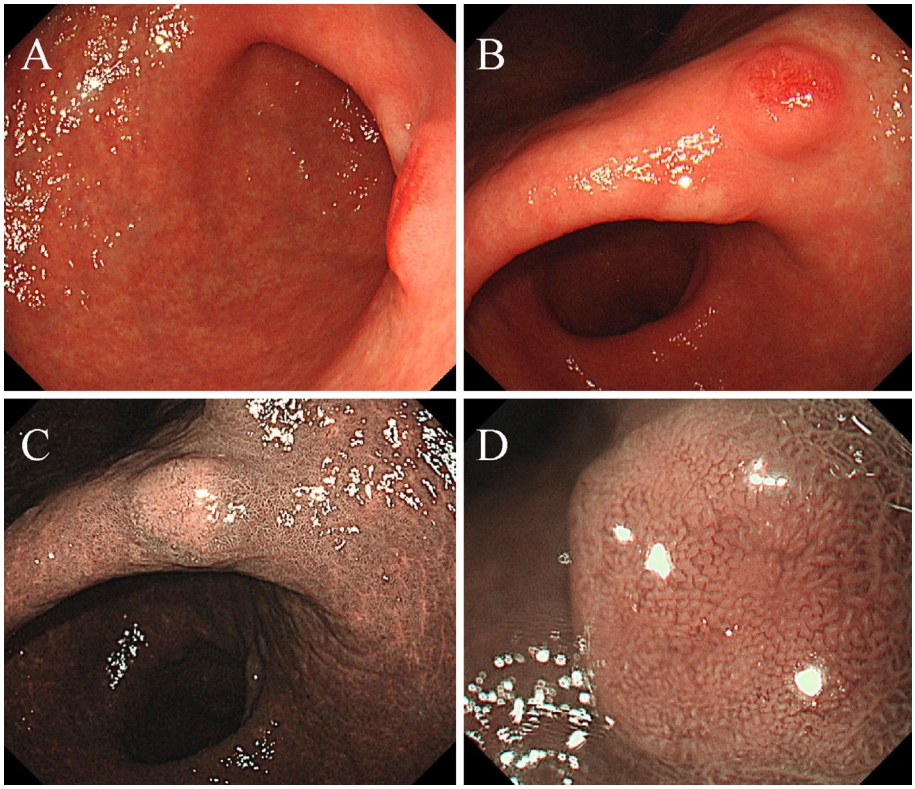

Figure 1. **Esophagogastroduodenoscopy. A whitish, superficial elevated lesion and a submucosal tumor with redness that appeared slightly centrally depressed in the posterior wall of the gastric angle on WLI (A, B). A whitish, superficial elevated lesion was depicted as a whitish, well-circumscribed superficial lesion by NBI (C). An irregular microvascular pattern was shown to be present within the demarcation line on magnifying NBI (D).**

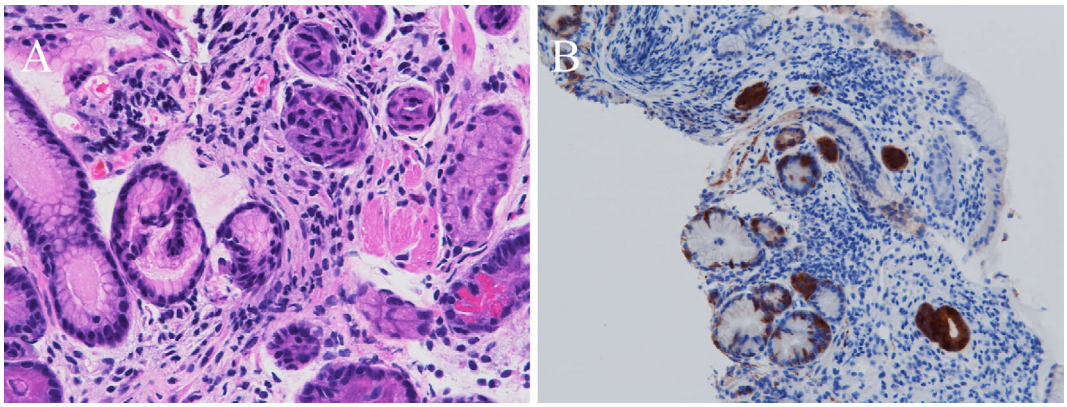

Figure 2. **A histopathologic examination and immunohistological staining of the biopsy specimen from the gastric wall. (A) Endocrine cell micronests were detected in the background gastric mucosa (Hematoxylin and Eosin staining). (B) Endocrine cell micronests were shown to be positive for synaptophysin.**

diagnosis. Macroscopically, the resected specimen was a 26×18-mm lesion with a negative margin (Fig. 3). A histological examination showed the lesion to be well-differentiated type (tub1) tubular adenocarcinoma (Fig. 4A) and NET G1 with submucosal invasion (Fig. 4C), with the latter shown to be positive for chromogranin A (Fig. 4D) and synaptophysin. ECMs were detected in the deep mucosal layer of the tubular adenocarcinoma (Fig. 4B). The gastric lesion in the patient was therefore diagnosed as synchronous 1) adenocarcinoma, type 0-IIa, measuring 6×4 mm, tub1, pT1a (M) and 2) NET, G1 measuring 8×8 mm, pT1b (SM). Each of these sections was shown to have negative margins. An EGD examination performed six months later revealed no signs of recurrence. In addition, a biopsy specimen revealed all other small NET-suspected lesions to be hyperplastic polyps.

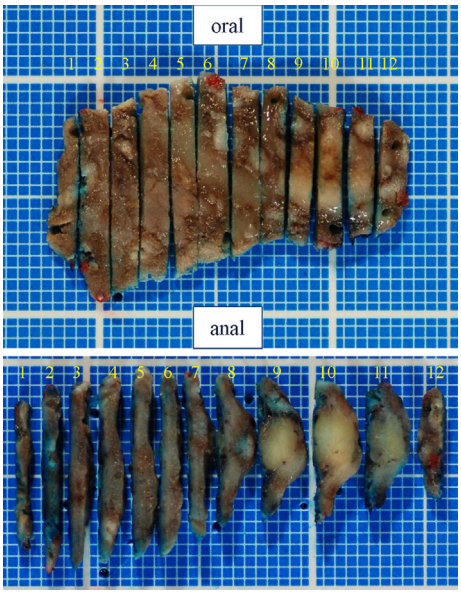

Figure 3. **Macroscopic view of the resected specimen. A 0-IIa adenocarcinoma (tub1) measuring 6×4 mm was shown to be present in sections 3-5, and a submucosal tumor measuring 8×8 mm was shown to be present in sections 9-11.**

Discussion

Our case has two important clinical implications. First, early gastric cancer/NET presented as a synchronous lesion amenable to resection with ESD. The endoscopic and pathological features of synchronous early gastric cancer/NET associated with autoimmune gastritis remain largely unclear, with no reports available in the literature.

In the 2010 WHO classification, gastrointestinal NETs are classified by the grade of malignancy of each component into NET G1, G2, and NECs (1). In addition, gastric NETs are categorized into three types: type I, NETs often seen in association with autoimmune chronic atrophic gastritis; type II, NETs associated with multiple endocrine neoplasia type 1 (MEN 1) and Zollinger-Ellison syndrome; and type III, aggressive NETs reported to occur only sporadically (3). It is recommended in the National Comprehensive Cancer Network (NCCN) guidelines for neuroendocrine tumors that type I and II gastric NET (≤2 cm) be managed with endoscopic resection, observation, or octreotide or lanreotide for symptom control in patients with Zollinger-Ellison syndrome (4), with endoscopic resection also recommended as a treatment option for small (≤1 cm) NET G1 lesions (5). While endoscopic mucosal resection (EMR) is the most

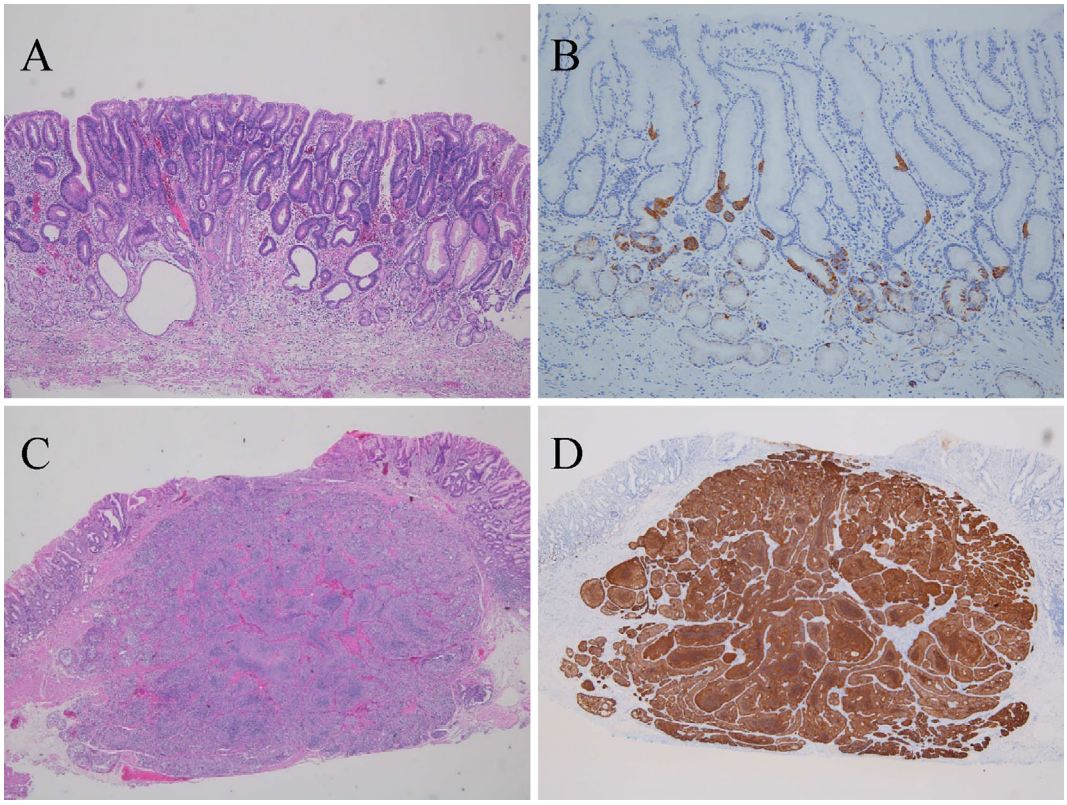

Figure 4. **Findings of a histopathologic examination and immunohistological staining of the lesions in the posterior wall. (A) The histological examination showed well-differentiated type (tub1) tubular adenocarcinoma (Hematoxylin and Eosin staining). (B) Endocrine cell micronests positive for synaptophysin were detected in the deep mucosal layer of the tubular adenocarcinoma. (C) The histological examination showed NET G1 with submucosal invasion (C), which was positive for chromogranin A (D).**

Table. Cases Reported to Date of Synchronous Gastric Cancer/NET in Autoimmune Gastritis.

					Gastric Cancer				NET					Treatment
No	Reference	Year	Age	Sex	Location	Type	Size (mm)	Depth	Histological type	Location	Grade	Number	Size (mm)	Depth	
1	(10)	2002	61	M	Lesser curvature of the upper gastric body	0-IIa+IIc	19×11	M	tub1	Lesser curvature of the upper gastric body	Unknown	2	Unknown	Unknown	Proximal Gastrectomy
2	(11)	2003	74	F	Anterior wall of the body	III	60×50	unknown	tub2	Anterior wall of the body	G1	1	2	SM	Distal Gastrectomy
3	(12)	2006	63	M	Lesser curvature of the body	0-IIb	30×20	M	sig	Greater curvature of the body	G1	1	7	MM	Distal Gastrectomy
4	(13)	2013	74	F	Anterior wall of the cardia	0-I	22×20	M	pap	Posterior wall of the fornix	G1	1	10	SM	Total Gastrectomy
5	Our case	2019	71	M	Posterior wall of the angle	0-IIa	6×4	M	tub1	Posterior wall of the angle	G1	1	8	SM	ESD

NET: neuroendocrine tumor, ESD: endoscopic submucosal dissection

commonly employed endoscopic procedure (6, 7), ESD is reported to be associated with similar resection rates and complication rates (8, 9) and is a more effective modality than EMR for resecting NETs, which are often shown to have invaded the submucosa, as it allows the resection area to be checked during incision, despite greater technical difficulties (8). In the present case, we decided to perform ESD for the following reasons: 1) the lesions were small gastric NETs measuring ≤1 cm; and 2) ESD would allow the two lesions to be resected in one attempt. Through ESD, the gastric cancer/NET lesion were completely resected with negative vertical margins. Thus far, four cases of synchronous gastric cancer/NET associated with autoimmune gastritis have been reported (Table) (10-13), all of which were diagnosed after total gastrectomy. To our knowledge, this is the first report describing synchronous early gastric cancer/NET that was amenable to complete resection with ESD.

The second implication of our case is that the synchronous early gastric cancer/ ET was derived from the same atrophic mucosa associated with autoimmune gastritis. Gastric cancer and NET lesions are reportedly observed in 0.9-9% and 4-9% of patients with autoimmune gastritis, respectively (14). The pathogenesis of gastric cancer is attributed to atrophic gastritis resulting in intestinal metaplasia (2) or long-term hypergastrinemia (15), leading to the development of adenocarcinoma, while that of type I gastric NET is attributed to elevated gastrin secretion in response to the loss of negative feedback by parietal cells, wherein hypo-/achlorhydria-induced hypergastrinemia results in enterochromaffin-like (ECL) cell hyperplasia and dysplasia, thus leading to type I gastric NET (16, 17). In our case, the patient was shown to be positive for anti-parietal cells, anti-intrinsic factor antibodies, and hypergastrinemia (gastrin, up to 1,440 pg/mL) but negative for serum *H. pylori* IgG antibody. Again, given that scattered ECMs were recognized in the background gastric mucosa and that no continuity was shown between the gastric cancer lesion and the NET, it was concluded that the synchronous early gastric cancer lesion/NET had been derived separately from the same atrophic mucosa associated with autoimmune gastritis.

In conclusion, early gastric cancer/NET G1 may present as a synchronous lesion derived from autoimmune gastritis. Patients with autoimmune gastritis require endoscopic surveillance for potential gastric cancer/NET.

The authors state that they have no Conflict of Interest (COI).

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