CASE REPORT

Multiple Gastric G1 Neuroendocrine Tumors with Venous and Lymphatic Invasion

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Abstract

A 60-year-old woman was admitted for the treatment of a gastric neuroendocrine tumor (NET) associated with type A chronic atrophic gastritis. The lesion measured 10 mm in diameter, and a computed tomography scan did not reveal any metastatic lesions. Endoscopic submucosal dissection (ESD) was subsequently performed. A histological examination revealed three gastric NETs, two of which exhibited vessel invasion. Endocrine cell micronests associated with a high risk of recurrence were also observed. Therefore, the patient underwent total gastrectomy with lymph node dissection. Because vessel invasion can occur in patients with small gastric NET G1, the use of ESD should be considered to carefully estimate the presence of invasion.

Key words: neuroendocrine tumor (NET), endocrine cell micronest (ECM), endoscopic submucosal dissection (ESD)


Introduction

The incidence of gastric neuroendocrine tumor (NET) has been increasing due to incidental discovery during screening esophagogastroduodenoscopy (EGD) for gastric diseases. The prevalence of gastric NETs is calculated to be 35 per 100,000 in the United States (1). Gastric NETs were referred to as gastric carcinoids until recently. Gastric carcinoids are classified into three types based on biological behavior. Type I develops in patients with type A chronic atrophic gastritis, type II is associated with Zollinger-Ellison syndrome or multiple endocrine neoplasia (MEN) type 1, and type III includes sporadic carcinoids (2).

In the 2000 World Health Organization classification, NETs are divided into three groups: well-differentiated neuroendocrine tumors, well-differentiated neuroendocrine carcinomas, and poorly-differentiated neuroendocrine carcinomas (3). Well-differentiated neuroendocrine tumors and poorly-differentiated neuroendocrine carcinomas refer to carcinoid tumors, while poorly-differentiated neuroendocrine carcinomas correspond to endocrine carcinomas in the Japanese Classification of Gastric Carcinoma (4). In the latest WHO 2010 classification, NETs are divided into G1 to G3 based on the rate of mitosis and the Ki-67 labeling index (5). However, lymphatic and venous invasion are not considered in this classification.

We herein present a case of type I gastric carcinoids (G1 gastric NET classified according to the WHO 2010) of <10 mm in diameter. Although the guidelines for gastric carcinoid suggest regular follow-up or endoscopic resection for such cases, our patient exhibited lymphatic and venous invasion and required total gastrectomy.

Case Report

A 60-year-old woman was detected as having a gastric polyp during mass screening for gastric cancer. Her history revealed hypothyroidism, and she took levothyroxine regularly. She had not previously received any proton pump inhibitors (PPIs) or H₂ receptor antagonists (H₂RAs). EGD revealed an elevated lesion in the anterior wall of the corpus of the stomach. The biopsy specimens demonstrated hyperplasia of enterochromaffin-like (ECL) cells. She was re-
ferred to our hospital for further examination and treatment of the gastric lesion.

EGD performed in our hospital revealed a submucosal tumor (diameter: 10 mm) with erosion (Fig. 1A, B). Immunohistochemical staining showed that the tumor was positive for chromogranin A, synaptophysin, AE1/AE3 and Grimelius: therefore, a diagnosis of gastric NET was made. A barium meal study showed a well-defined 0-IIa-like lesion with a slight depression in the anterior wall of the corpus. A computed tomography (CT) scan of the abdomen and pelvis did not reveal any evidence of metastatic lesions. The patient was admitted to our hospital for endoscopic submucosal dissection (ESD). On admission, she had no carcinoid symptoms including blushing of the skin or diarrhea. The results of the peripheral blood and blood chemistry examinations were within the normal limits. The serum level of gastrin was >3,000 pg/mL (normal range, 0-200), whereas both anti-parietal cell antibody and intrinsic factor antibody tests were negative. The patient had never received eradication therapy for Helicobacter pylori infection and an H. pylori stool antigen test was negative.

We performed en bloc resection via ESD without complications. The resected specimen measured 28×29 mm in diameter. A histological examination revealed that three G1 gastric NETs (Figs. 1C, 2A-C, 3A), two of which exhibited lymphatic and/or venous invasion (Figs. 2D, E, 3B, C). Multiple endocrine cell micronests (ECMs) were also observed in the resected specimen (Fig. 4A, B). The patient was considered to be at a high risk for recurrence, and total gastrectomy with lymph node dissection was performed after obtaining informed consent. In the surgically resected stomach, another NET was also identified (pT1b2 [SM 700 μm], med, INFb, ly0, v0, pPM0, pDM0, 3 mm) on the near proximal side of the ESD scar. The resected lymph nodes showed no evidence of metastasis. Twenty-two months since the operation, there has been no clinical evidence of recurrence.

Discussion

Gastric NETs are referred to as gastric carcinoids and classified into three types (2). The guidelines for treating gastric carcinoids recommend different treatments for each type (2). For type I and II gastric carcinoids, gastrin continuously stimulates the proliferation of ECL cells, and malignant transformation occurs in the fundic glands (3). Hypergastrinemia is associated with multiple gastric ECMs and gastric carcinoids (6). However, hypergastrinemia and multiple gastric NETs can occur without type A gastritis, Zollinger-Ellison syndrome or MEN type 1 (7). These conditions may be associated with proton pump deficiencies in gastric parietal cells. Clinically, gastric NET has become more prevalent since the development of PPIs (8). Gastric carcinoids may occur after the long-term suppression of gastric acid by both PPIs and H2RAs. In our case, the gastric NET was associated with type A chronic atrophic gastritis
Figure 2. (A) Histological examination of the main tumor (Fig. 1C-m). Hematoxylin and Eosin staining (H&E staining) showing that the tumor was composed of nuclei that possessed chromatin, arranged in cords and small nests proliferated in the mucosal and submucosal layers. The tumor was positive for chromogranin A (B) and partially positive for neuron-specific enolase (C). Invasion into the lymphatic vessel was observed on H&E staining (D) and D2-40 staining (E). The Ki-67 (MIB-1) labeling index was 1%. The histological diagnosis was pT1b (SM, 4000 μm), med, INFa, ly (+), v (-), pHM0, pVM0.

Figure 3. Histological findings of sublesion 1 (Fig. 1C-s2). (A) H&E staining showing the same appearance as the main tumor. Invasion into the submucosal vein was observed on H&E staining (B) and elastic-van Gieson staining (C).

because there were multiple ECMs and severe atrophy in the gastric fundic glands without H. pylori infection or the use of acid suppressants. Antibodies against parietal cells and anti-intrinsic factor antibodies are not always detected in patients with type A gastritis. Anti-parietal cell antibodies and anti-intrinsic factor antibodies have been reported to be positive in 60-90% and 70% of patients with type A chronic atrophic gastritis, respectively (9, 10). Therefore, we classified this case as type I gastric carcinoid, even though the tests for anti-parietal cell antibodies and intrinsic factor anti-
bodies were negative. Type I gastric carcinoids are considered to have a lower metastatic potential. Rindi et al. demonstrated that metastasis occurred in two of 41 patients with type I gastric carcinoids, three of 10 patients with type II gastric carcinoids and 10 of 14 patients with type III gastric carcinoids (11). Although no tumor-related deaths were observed in the patients with type I gastric carcinoids, tumor-related deaths occurred in one and seven patients with type II and III gastric carcinoids, respectively (11). Rappel et al. showed that no lymph node or distant metastasis occurred in any of 88 patients with type I gastric carcinoids, although metastasis was observed in two of 12 patients with type III gastric carcinoids (12). Although the present case was considered to be a case of type I gastric carcinoids, two of three gastric carcinoids exhibited lymphatic or venous invasion.

Surgery is also performed for larger gastric NETs (carcinoids). In Japan, surgery is the standard therapy for gastric NETs measuring >10 mm in diameter (13). In most European countries, surgery is recommended for any gastric NET >20-30 mm in diameter (14). Normalization of the serum gastrin via antrectomy has also been performed to reduce gastric carcinoids, although its efficacy remains controversial. After antrectomy, it is necessary to perform follow-up endoscopy every six or 12 months.

The latest European guidelines for the management of gastric NET were published in 2005 (15). According to these guidelines, because metastasis of type I gastric NET is infrequent, follow-up is appropriate for small lesions, although limited surgery is preferable (15). In a recent study, endoscopic therapy was adapted to treat type I gastric NET measuring 10 mm or smaller in diameter and consisting of less than six nodules within the submucosal layer (14). In the present case, although the gastric NETs were type I and <10 mm in diameter, the resected specimen demonstrated lymphatic and venous invasion in the main tumor and one of the sublesions. A recent case report showed that a 60-year-old man died from type I G1 gastric NET (16). In that case, although the size of the gastric NET was 12 mm in diameter and the Ki-67 index was less than 2%, there were liver and peritoneal metastases. Lymphatic and venous invasion may also have occurred, as in our case. In addition, in the present case, there were multiple ECMs in the resected stomach. ECMs are primarily composed of ECL cells, such as NETs. ECMs have a trabecular or ribbon-like structure and frequently infiltrate into the muscularis mucosae or submucosa (17). The presence of multiple ECMs is associated with a higher risk of gastric NET recurrence (17), and a total gastrectomy was performed in the present case.

In conclusion, there are currently no treatment guidelines for gastric NET based on the 2010 WHO classification. In this case report, we demonstrated that lymphatic and venous invasion can occur in patients with small G1 gastric NETs. Therefore, even in cases of small gastric NETs, ESD should be performed in order to carefully estimate the presence of lymphatic and venous invasion. The use of follow-up CT is also necessary to evaluate metastasis after successful ESD.

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

References
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