Synchronous Triple Gastric Cancer Incorporating Mixed Adenocarcinoma and Neuroendocrine Tumor Completely Resected with Endoscopic Submucosal Dissection

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Abstract:
The endoscopic and pathological features of early gastric mixed adenoneuroendocrine carcinoma (MANEC), as well as its carcinogenesis, remain largely unclear. Screening esophagogastroduodenoscopy was performed on an 80-year-old man, revealing 3 superficial elevated lesions. Endoscopic submucosal dissection (ESD) was performed, and the patient was diagnosed with intramucosal gastric cancer comprising mixed adenocarcinoma and neuroendocrine tumor, well-differentiated adenocarcinoma and well-differentiated adenocarcinoma, with negative margins. To our knowledge, this is the first report describing the endoscopic and pathological findings of synchronous triple gastric cancer incorporating mixed adenocarcinoma and neuroendocrine tumor completely resected with ESD.

Key words: Gastric MANEC, Gastric triple carcinoma, Endoscopic treatment

Introduction

Mixed adenoneuroendocrine carcinoma (MANEC) (1) is a tumor composed of both adenocarcinoma and neuroendocrine carcinoma (NEC) components, with each comprising at least 30% of the lesion. La Rosa et al. (2) classified MANECs into high-grade tumors composed of adenocarcinoma and neuroendocrine carcinoma (NEC) and intermediate-grade tumors composed of mixed adenocarcinoma and G1/G2 neuroendocrine tumor (NET). The endoscopic and pathological features of early gastric MANEC remain poorly described.

We herein report a case of synchronous triple gastric cancer incorporating MANEC completely resected with endoscopic submucosal dissection (ESD).

Case Report

Screening esophagogastroduodenoscopy (EGD) was performed on an 80-year-old man, revealing 3 superficial elevated lesions in the anterior wall of the middle gastric body, the posterior wall of the gastric angle, and the lesser gastric body (Fig. 1A-D). The patient was shown to be positive for serum IgG antibody to Helicobacter pylori but negative for anti-parietal cells and anti-intrinsic factor antibodies, suggesting the presence of H. pylori-associated atrophic gastritis.

ESD was performed on suspected well-differentiated tubular adenocarcinoma (Fig. 2A-C). Histologically, the tumor in the anterior wall showed two distinct components of tubular adenocarcinoma and NET G1/G2 neuroendocrine tumor (NET). The endoscopic and pathological features of early gastric MANEC remain poorly described.

The patient was thus eventually diagnosed with intramu-
Figure 1. Esophagastroduodenoscopy. (A) A superficial elevated lesion in the anterior wall of the middle gastric body; (B) chromoendoscopy with indigo carmine showing the border of the lesion; (C) superficial elevated lesions in the posterior wall of the gastric angle and the lesser gastric body and (D) chromoendoscopy with indigo carmine showing the border of the lesions.

Figure 2. A macroscopic view of the resected specimen. (A) The lesion in the anterior wall of the middle gastric body was 0-IIa 25×22 mm, (B) the lesion in the posterior wall of the gastric angle was 0-IIa 11×9 mm, and (C) the lesion in the posterior wall of the lesser gastric body was 0-IIa 12×12 mm.
margins. *H. pylori* was successfully eradicated after ESD.
EGD and computed tomography examinations six month later revealed no recurrence or metastasis.

**Discussion**

Two important clinical issues emerged in our case. First, gastric MANEC may present as an intramucosal lesion. According to recent reports, gastric MANEC presents as an advanced tumor in most cases and is associated with a poor prognosis even when surgically treated (3). In 1987, Lewin (4) proposed the classification of gastrointestinal tumors with exocrine and neuroendocrine components as follows: 1) collision tumors, 2) combined tumors and 3) amphi-crine tumors.

Under the 2010 WHO classification, MANEC (1) is a tumor composed of both adenocarcinoma and NEC components, with each comprising at least 30% of the lesion. La Rosa et al. (2) classified MANECs as high-grade tumors composed of adenocarcinoma and NEC and intermediate-grade tumors composed of mixed adenocarcinoma and G1/G...
2 NET, according to the grade of malignancy of each component. The present lesion was mixed adenocarcinoma and NET G1, which was compatible with intermediate-grade MANEC. To date, three cases of ESD-resected gastric high-grade MANEC have been reported (5-7) (Table). However, of these, only one was classified as an intramucosal lesion in terms of the histological depth, with the other two classified as submucosal lesions. Therefore, the endoscopic and pathological features of early gastric MANEC remain poorly described. Furthermore, the carcinogenesis of MANEC remains unclear. At least two possible hypotheses have been proposed: 1) the partial differentiation of adenocarcinoma into neuroendocrine cells (8) and 2) the bidirectional transformation of monoclonal pluripotent epithelial stem cells into adenocarcinoma and neuroendocrine cells (9). In the present case, the components of adenocarcinoma and NET showed a clear tissue distribution but merged into each other at the border. A case of mixed adenocarcinoma and NET G1 of the rectum was recently reported to have likely differentiated from common putative precursor cells bi-directionally.

In conclusion, gastric mixed adenocarcinoma and NET G1 may arise from a background of H. pylori-associated chronic gastritis. In a case of mixed adenocarcinoma and NET G1 completely resected with ESD, hypergastrinemia was thought likely to be derived from H. pylori-associated chronic gastritis (12). Reports of type I gastric NET with hypergastrinemia following H. pylori-associated chronic gastritis have also been published (13, 14). In our case, the patient was shown to be positive for serum IgG antibody to H. pylori but negative for anti-parietal cells and anti-intrinsinc factor antibodies, and blood tests 2 months after the withdrawal of vonoprazan revealed hypergastrinemia (gastrin, up to 1,360 pg/mL).

In addition, given that endocrine cell hyperplasia and endocrine cell micronests were not recognized in the background gastric mucosa, hypergastrinemia following H. pylori-associated atrophic gastritis was thought likely to be responsible for the condition. We therefore concluded that synchronous triple gastric cancer incorporating gastric mixed adenocarcinoma and neuroendocrine tumor all developed against a background of H. pylori-associated chronic gastritis. To our knowledge, this is the first report describing gastric mixed adenocarcinoma and type I NET G1 probably derived from H. pylori-associated chronic gastritis.

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

Disclosure statement
The authors have no conflicts of interest to disclose in association with this study.

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