—Case Reports—

A Case of Multiple Gastric Carcinoids That Could Not Be Preoperatively Diagnosed

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Abstract

Here, we report the case of patient with multiple gastric carcinoids showing histopathological behavior similar to that of type I carcinoid tumors of the stomach. The patient was a 61-year-old man diagnosed as having a gastric tumor, which was revealed by follow-up computed tomography. Upper gastrointestinal endoscopy revealed a protruded tumor in the greater curvature and a small polyp in the anterior wall of the upper stomach. A biopsy revealed gastric carcinoid. Because he refused to be operated for gastric carcinoid, upper gastrointestinal endoscopy was performed 5 months later. A malignant transformation of the gastric carcinoid was strongly suspected. Therefore, the patient was admitted for operation. Laboratory findings were normal. With the diagnosis of type III gastric carcinoid, total gastrectomy was performed. Microscopic examination revealed that the carcinoid tumor was confined to the submucosa and that the small polyp mentioned earlier was also a carcinoid. Microcarcinoids and numerous enterochromaffin-like cell hyperplasias were observed along the muscularis propria of the fundus. The tumor differed from typical type I gastric carcinoids in several ways. Immunohistochemical staining for chromogranin A, synaptophysin, and cytokeratin was positive. However, p53 was absent, and the MIB-1 index was low. Two years after surgery, the patient is alive without recurrence.
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Key words: multiple gastric carcinoids, enterochromaffin-like cell hyperplasia

Introduction

Recently, the diagnosis of carcinoid tumors of the stomach has been increasing because of the pathologists' increased awareness of these lesions, the widespread use of endoscopy in gastroenterology practice, and the extensive use of proton-pump inhibitors[1]. Rindi et al. have classified gastric carcinoid tumors into three subtypes on the basis of clinicopathologic characteristics[2]. Type I is associated with chronic atrophic gastritis type A.

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Type II is associated with the Zollinger-Ellison syndrome (ZES) and multiple endocrine neoplasia type 1 (MEN-1). Type III is associated with sporadic gastric carcinoids and is considered far more aggressive than either type I or II. Here, we describe a patient with multiple gastric carcinoids showing histopathological behavior similar to that of type I carcinoid tumors of the stomach. However, in some respects, its behavior deviated from the classification.

Case Report

A 61-year-old man was referred to the department of surgery because of a gastric tumor, found on follow-up computed tomography (CT) in December 2004. One month earlier, he had undergone total cystectomy with ileal conduit because of urinary bladder cancer. Upper gastrointestinal endoscopy (UGE) revealed a protruded tumor in the greater curvature (**Fig. 1a**) and a small polyp in the anterior wall of the upper stomach. Biopsy revealed gastric carcinoid. The patient refused surgery for the gastric carcinoid and was discharged 2 days after UGE. Five months later, UGE was repeated. An ulcerated surface tumor of approximately 2.5 cm was observed in the greater curvature of the stomach (**Fig. 1b**). Because a malignant transformation of gastric carcinoid was strongly suspected, the patient was admitted to our hospital for operation. He was asymptomatic. On the other hand, his brother had died of hepatocellular cancer. Laboratory findings were normal. Abdominal CT showed no metastatic lesions. With the diagnosis of gastric carcinoid, total gastrectomy was performed in May 2005. On macroscopic examination, the tumor showed an irregular shape with an ulceration of the greater curvature and another small sessile polyp in the anterior wall of the upper stomach. Microscopic examination showed that the tumor was composed of oval- to polygonal-shaped cells with round nuclei, exhibited various growth patterns (trabecular, medullary, and pseudoglandular patterns), and was confined to the submucosa (**Fig. 2a**). The small polyp in the anterior wall was also a carcinoid (**Fig. 2b**). Numerous enterochromaffin-like (ECL) cell hyperplasias were observed along the mucosal muscular layer, throughout the fundus (**Fig. 2c, d**). Antral G cells were hyperplastic. According to the updated Sydney System for the classification of gastritis, chronic gastritis of the corpus with moderate to severe atrophy and intestinal metaplasia was observed. Mild *Helicobacter* (*H*) *pylori* infection and mild neutrophile infiltration were also observed[3]. The characteristics of the chronic gastritis in this patient are shown in **Table 1**. Retrospectively, chronic atrophic gastritis was predominantly found in the corpus with UGE. Immunohistochemical staining for chromogranin A, synaptophysin, and cytokeratin was positive. P53 was absent and the MIB-1 index was low. Gastrin was positive in antral hyperplastic G cells (**Fig. 2e**). To investigate the distribution of carcinoid tumors, we mapped the lesions of the entire stomach (**Fig. 3**). As a result, microcarcinoids that had not been visible macroscopically were also found. No postoperative complications were observed, and the patient was discharged 15 days after surgery. Two years after surgery, he is alive without recurrence.

Discussion

Gastric carcinoid tumors were previously considered rare lesions, representing less than 1% of all gastric tumors. Recently, gastric carcinoid tumors have been increasing in incidence, and now account for 1.77% of all gastric tumors[4]. The reason for this increased detection rate is the widespread use of endoscopy, the applications of immunohistochemical methods, and the worldwide use of proton-pump inhibitors[1].

Rindi et al. have characterized three clinicopathologic subtypes of gastric carcinoid tumors[2]: type I, associated with type A chronic atrophic gastritis (CAG/A); type II, associated with ZES and MEN-1; and type III, associated with sporadic gastric carcinoids. Type I and II lesions are associated with hypergastrinemia. Type I is the most common and comprises approximately 70% to 80% of all gastric carcinoids. The lesions are localized in the atrophic oxyntic mucosa (fundus or

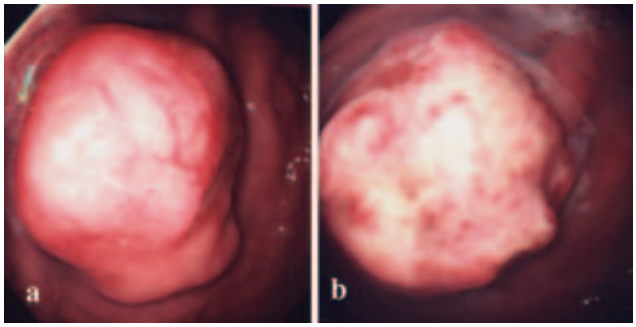

Fig. 1 **a**: Endoscopic appearance of a carcinoid tumor in the greater curvature of the upper body of the stomach. **b**: Endoscopic appearance of the carcinoid tumor 6 months after the first endoscopic examination.

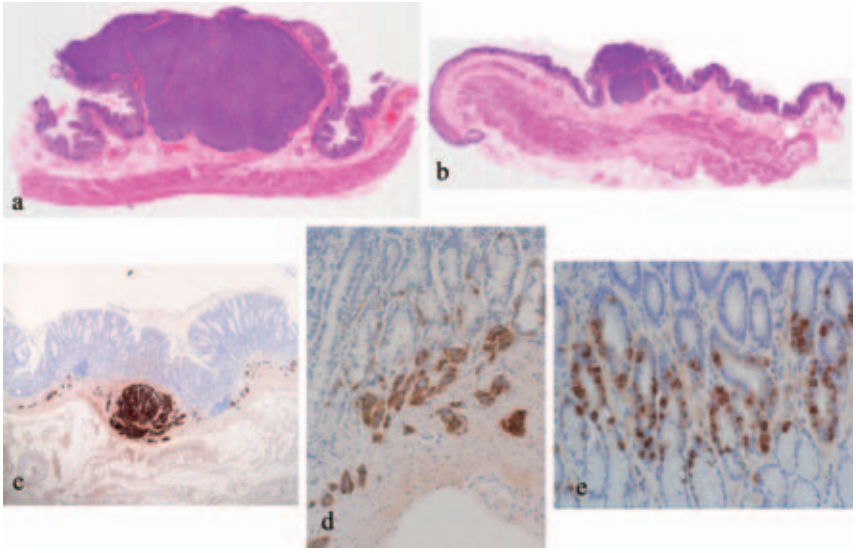

Fig. 2 **a**: Microscopic findings of carcinoid tumor in the greater curvature of the upper body of the stomach. The carcinoid tumor had invaded the submucosa. **b**: Microscopic findings of a carcinoid tumor in the anterior wall of the upper body of the stomach. **c**: Microscopic findings of numerous ECL cell hyperplasias along the lamia muscularis mucosa of the fundus. **d**: Multiple ECL cell hyperplasias observed in the lamina propria. **e**: Immunohistochemical staining for gastrin in antral hyperplastic G cells.

body) of patients with CAG/A with or without pernicious anemia. Characteristically, the lesions are multicentric, small, and polypoid and tend not to metastasize. Type II, associated with ZES and MEN-1, accounts for 5% to 10% of all gastric carcinoids. Lesions are usually multiple and small. Unlike type I lesions, they occur equally in men and women at the average age of 50. Their clinicopathological behavior is intermediate, between that of types I and III lesions. Type III is less common (15% to 20%) but is characterized by invasiveness and metastases. Type III carcinoids are usually large, solitary lesions that evolve in normal gastric mucosa having normal gastrin levels[1]. In our patient, the large tumor on the

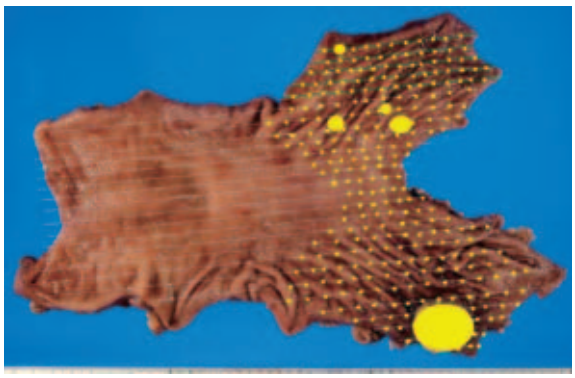

Fig. 3 Scheme of the resected specimen, determined by mapping of the entire stomach. Points indicate the lesions of ECL hyperplasia (small yellow oval points) and carcinoids (large yellow points).

Table 1 Degree of gastric atrophy according to Updated Sydney System

	Upper body	Angle	Antrum
Inflammation	1−2	2	1
Activity	1	1	0
Atrophy	3	2	0−1
Intestinal metaplasia	2	1	0
H. pylori	1	1	1

0: normal, 1: mild, 2: mopderate, 3: marked

greater curvature of the stomach was about 2.7 cm in size, and a small polyp at the anterior wall was not diagnosed as carcinoid during the first endoscopic examination. Moreover, no lesions that suggested the presence of MEN-1 or ZES. Five months after the initial diagnosis, the tumor had ulcerated, suggesting a malignant transformation of the gastric carcinoid. Thus, type III gastric carcinoid was diagnosed preoperatively.

Gilligan et al. have proposed a decision tree for the management of gastric carcinoid tumors[5]. Type III sporadic carcinoids require aggressive surgery. Lesions of types I or II can be initially managed with endoscopic excision, if they are smaller than 1 cm, do not extend beyond the submucosa, and are fewer than five, with endoscopic follow-up every 6 to 12 months. According to the decision tree, our patient should have undergone total gastrectomy with lymph node dissection. Histological analysis revealed that the tumors were carcinoid tumors and that numerous ECL cell hyperplasias were present along the mucosal muscular layer throughout the fundus **(Fig. 3)**. The final pathological diagnosis was multiple gastric carcinoids similar to type I gastric carcinoid. On the basis of the findings of endoscopy, type III gastric carcinoid was diagnosed. A differential diagnosis between a single and large type I gastric carcinoid and a type III gastric carcinoid was difficult because the clinical data was insufficient. If gastric carcinoid is found in the upper body, biopsies of the tumor and the mucosa near the tumor are required, which offer useful information for the typing of gastric carcinoid tumors.

Safatle-Ribeiro et al. have reported that p53 immunoexpression associated with a high proliferative rate (Ki-67) is useful for distinguishing between types I and III gastric carcinoid tumors[6]. Type I carcinoid show no positive staining for p53. In our patient's tumor, p53 was negative. Moreover, MIB-1, which is a true anti-Ki-67 equivalent, was low in the tumor. These results indicated that the tumor did not show a biologically aggressive growth pattern and had the features of type I gastric carcinoid.

Here, we have described a patient with multiple gastric carcinoids showing histopathological behavior similar to that of type I gastric carcinoid tumors of the stomach. However, in some respects, its behavior deviated from Rindi's classification.

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