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CASE REPORT

Gastric carcinoid in a patient infected with *Helicobacter pylori*: A new entity?

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Abstract

There are four types of gastric carcinoid tumors, classified according to their histology and malignant potential. Only a few cases of carcinoid tumors in patients infected with *Helicobacter pylori* (*H. pylori*) have been reported so far. We report a patient infected with *H. pylori* presenting with a small solitary gastric carcinoid tumor with very low proliferative rate and normal gastrin levels. The tumor was endoscopically removed and the patient received an eradication therapy against *H. pylori*. No signs of metastatic disease have been found so far during more than 3 year of follow-up. Infection with *H. pylori* may cause chronic gastritis with normal or elevated gastrin levels, leading to the development of gastric carcinoids by mechanisms unrelated to gastrin. Enterochromaffin-like cell tumors related to a chronic *H. pylori* infection may be considered as a distinct type of gastric carcinoid tumors.

Key words: Gastric carcinoids; Gastrin; Gastritis; *Helicobacter pylori*

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INTRODUCTION

Gastric carcinoids are rare neuroendocrine tumors of the stomach that arise from the enterochromaffin-like (ECL) cells[1]. Initially, three types of gastric carcinoids were reported[2,3]. The first two types, which are multiple, are related to high gastrin levels; type Ⅰ arise in patients with autoimmune chronic atrophic gastritis type A and type Ⅱ occur in patients with the Zollinger-Ellison Syndrome. Type Ⅲ is a solitary tumor with no known correlation to gastrin production. More recently a highly aggressive variant has been described, named type Ⅳ gastric carcinoid tumor[1].

Helicobacter pylori (*H. pylori*) has been reported to cause chronic atrophic gastritis[4] and alteration of the gastric secretion[5]. Chronic gastritis caused by *H. pylori* can be a risk factor for gastric cancer[4], but the occurrence of ECL cell tumors in the stomach of patients infected with *H. pylori* is rare[6]. We here present a patient infected with *H. pylori* presenting with a solitary gastric carcinoid tumor.

CASE REPORT

A 60-yr-old woman from Sweden had been suffering from abdominal pain for several years and flushing since 2003. She had no family history for MEN I, Zollinger-Ellison syndrome or autoimmune gastritis. Gastroscopy in May 2006 due to oral lichen showed a polyp-like lesion in the

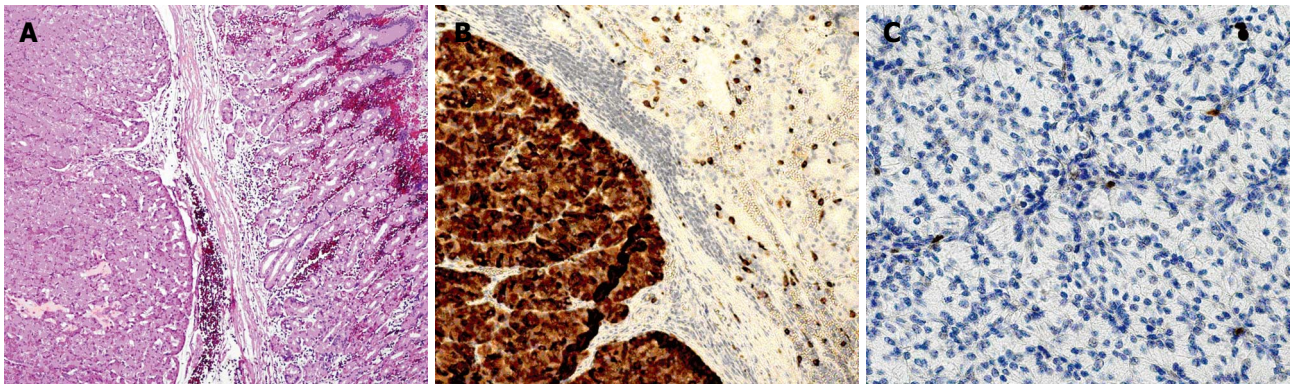

Figure 1 Gastric carcinoid. A: Infiltration of the muscularis mucosae; Hematoxylin-eosin stain. Magnification, × 50; B: Tumor and normal mucosa adjacent to tumor immunostained for VMAT-2. Virtually all tumor cells positive. Magnification, × 100; C: Tumor immunostained for Ki-67. < 1% tumor cells positive. Magnification, × 200.

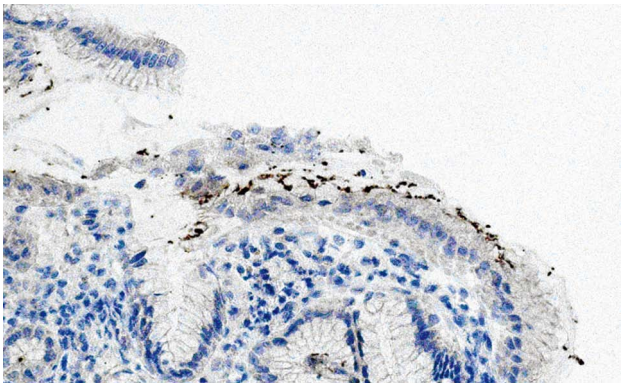

Figure 2 Signs of *Helicobacter pylori* infection in biopsy from antral mucosa. Magnification, × 200.

gastric body near the cardia. Microscopic examination showed a neuroendocrine tumor positive for chromogranin A, VMAT-2 and synaptophysin, and with serotonin positivity in the majority of the cells. Ki67 was positive in < 1% of the tumor cells (Figure 1). The tumor was considered to be a type Ⅲ ECL-oma. Inflammation and *H. pylori* were present in the gastric mucosa (Figure 2). The patient was referred to our Department and a new gastroscopy in September 2006 showed inflammation in the antrum, corpus and fundus, atrophy in the antrum and corpus, and ECL-cell hyperplasia in the corpus, where a polyp considered as ECL-oma of type Ⅰ was found. Gastroscopy in November 2006 showed gastritis and positivity for *H. pylori* but no ECL hyperplasia. Gastric pH was 3.5. The patient had normal urinary histamine metabolites, normal U-5'HIAA, normal fasting serum gastrin and normal plasma chromogranin A and B. She received eradication treatment against *H. pylori*. A gastroscopy in February 2007 showed chronic inflammation without atrophy in the mucosa. There was a 0.5 cm polyp in the upper corpus surrounded by ECL hyperplasia. The tumor cells were positive for chromogranin A and VMAT 2, but negative for serotonin. Ki67 was < 1%. The tumor was considered to be a type Ⅲ ECL-oma due to lack of mucosal atrophy. The patient underwent an endoscopic mucosal resection of the polyp in April 2007. The pathology report showed a 7 mm ECL cell carcinoid with 5 mm depth that did not invade the muscularis propria. The tumor cells were positive for chromogranin A, synaptophysin and VMAT-2 but negative for gastrin and serotonin; Ki67 was < 1%. The tumor was considered as a type Ⅲ ECL-oma. A gastroscopy in September 2007 showed inflammation in the antrum with focal metaplasia but no signs of *H. pylori*, and another gastroscopy in December 2008 showed no inflammation or atrophy. The patient has not had any signs of metastatic disease in the liver or elsewhere. Repeated CT scans and ultrasounds, as well as an octreoscan in 2006 and a 5-HTP PET scan in January 2008, have been negative. Urinary 5-HIAA, plasma chromogranin A and B and serum gastrin and pancreatic polypeptide have been normal at all control visits. She has no evidence of pernicious anemia and thyroid hormone levels have been normal. At the latest control visit in January 2010, gastroscopy was macro- and microscopically normal. Staining for *H. pylori* was negative.

DISCUSSION

We report a patient with normal gastrin levels presenting with a small solitary gastric carcinoid with very low proliferative rate and without evidence of metastatic disease during more than 3 years of follow-up. The normal gastrin levels suggest that the carcinoid tumor was not type Ⅰ or Ⅱ. The absence of metastatic disease and the small dimension of the polyp, together with the low proliferative rate, indicate that it was not a type Ⅲ carcinoid. The patient was infected with *H. pylori* and had signs of chronic gastritis, gastric atrophy and ECL cell hyperplasia, which resolved after eradication of the *Helicobacter* infection. There have been no recurrences after the eradication treatment and endoscopic polypectomy. Although careful interpretation is needed, a causal relationship seems plausible. It is well known that chronic acid suppression may induce ECL cell proliferation[7]. However, our patient did not receive any proton pump inhibitors or other acid suppressive therapy, neither before the development of the carcinoid tumor nor during the follow-up period. It has previously been shown that longstanding *H. pylori* infection causes chronic inflammation of the gastric mucosa in animals[8]. A long-term *H. pylori* infection is also associated with atrophy of the gastric mucosa, and atrophy is a

risk factor for malignancy[4]. *H. pylori*-induced gastritis may play an important role in the development of gastric adenocarcinoma in humans[4] and animal models[9]. Development of gastric carcinoid tumors in subjects infected with *H. pylori* is believed to be rare[6], but has been described in animals[9-11] and, more rarely, in humans. Five humans infected with *H. pylori* without atrophic gastritis or Zollinger-Ellison syndrome who developed gastric carcinoids have been reported in Japan[12]. In Europe, Solcia reported four cases[13] of gastric carcinoids in *H. pylori*-infected humans, of whom all had chronic atrophic gastritis type A. Infection with *H. pylori* was, however, found to be much more common in patients with early gastric carcinomas than in carcinoid patients[13]. *H. pylori* thus seems more likely to cause neoplasms with higher malignant potential than the indolent carcinoids. Since the chronic gastritis in our patient resolved and no tumor recurrences have occurred after eradication treatment, it is nevertheless possible that her gastric carcinoid was actually caused by *H. pylori*-induced chronic gastritis.

H. pylori may affect the acid secretion of the parietal cells by causing mucosal inflammation[14]. Gastric acid secretion depends on the localization and the degree of the inflammation[14]. Acute infection with *H. pylori* results in hypochlorhydria, whereas chronic infection can cause either hypo- or hyperchlorhydria, depending on the distribution of the infection and the degree of corpus gastritis[5]. Recent studies suggest that inflammatory cytokines, produced in response to the bacteria, can play a role in the perturbations in acid and gastrin secretion induced by *H. pylori* [5]. Gastrin is associated with enterochromaffin-like (ECL) cell proliferation and is a factor implicated in the pathogenesis of ECL-cell tumors type Ⅰ and Ⅱ[3]. The patients in Japan with *H. pylori*-associated gastric carcinoids mentioned above all had high gastrin levels. Our patient, however, developed ECL-cell hyperplasia and a gastric carcinoid tumor despite normal gastrin levels. This observation suggests that *H. pylori* may facilitate gastric ECL cell proliferation by other mechanisms, independent of gastrin hypersecretion. The mucosal inflammation induced by *H. pylori* has been shown to cause excessive apoptosis, which in turn leads to proliferation[15,16]. Lipopolysaccharides also appear to influence tumor ECL cell proliferation[16,17]. Another factor involved in ECL cell proliferation is REG protein, which may be produced by *H. pylori* infection[18].

In conclusion, we postulate that *H. pylori* may lead to chronic gastritis, with normal or elevated gastrin levels, and cause the development of gastric carcinoids by mechanisms unrelated to gastrin. ECL cell tumors related to a chronic *H. pylori* infection may be considered as a distinct type of gastric carcinoid tumors, as they seem to have distinct histopathological, pathogenetic and clinical characteristics compared to the other types of gastric carcinoids.

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