

# Hyperplastic polyposis and cancer of the colon with gastrinoma of the duodenum

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## SUMMARY

**Background** A 64-year-old woman presented to the emergency room with a 3-month history of intermittent abdominal cramps, accompanied by nausea, vomiting, anorexia, and decreased bowel movements consistent with a partial intestinal obstruction. She had a 12-year history of peptic ulcers, which had been treated with histamine-2 blockers.

**Investigations** Physical examination, abdominal X-ray, abdominal CT scan, colonoscopy and assessment of gastrin levels.

**Diagnosis** Duodenal neuroendocrine neoplasm showing gastrin expression and stage III (T3N2M0), poorly differentiated adenocarcinoma of the cecum arising from hyperplastic polyposis.

**Management** Right-sided hemicolectomy with ileocolonic anastomosis, duodenal resection, leucovorin and 5-fluorouracil chemotherapy, annual colonoscopic surveillance, and polypectomy.

**KEYWORDS** adenoma, colorectal cancer, gastrinoma, hyperplastic polyposis, Zollinger–Ellison syndrome

## CME

This article offers the opportunity to earn one Category 1 credit toward the AMA Physician's Recognition Award.

## THE CASE

A 64-year-old woman presented to the emergency room in March 1997 with a 3-month history of intermittent, right-lower-quadrant cramps occurring approximately 30 minutes postprandially. These cramps were accompanied by nausea, vomiting and anorexia. The patient also experienced fatigue and had lost 6 kg of weight over a 2-month period. Approximately 1 week prior to presentation, she experienced increased severity of pain with a decrease in bowel movements. This constellation of symptoms was consistent with a partial intestinal obstruction. There was no significant family history of disease, but the patient had a 12-year history of peptic ulcers treated with histamine-2 blockers, which alleviated, but did not completely control, her watery stools. In 1991, abdominal CT scan, gastroscopy, colonoscopy, and small bowel follow-through were unremarkable and no further treatment was given at this time.

At presentation in March 1997, an abdominal X-ray demonstrated multiple air-fluid levels suggestive of a small-bowel obstruction. An abdominal CT scan demonstrated a mass in the third part of the duodenum, as well as sessile lesions in the ileocecal region and ascending colon. A colonoscopy performed 5 days after presentation confirmed the presence of a cecal mass and revealed multiple colonic polyps. Gastrin levels were 1,393 ng/l (normal range: 0–110 ng/l), which was consistent with a diagnosis of ZOLLINGER–ELLISON SYNDROME (ZES). A right hemicolectomy with ileocolonic anastomosis, and a duodenal resection, were performed during a single operative procedure 8 days following presentation. The excised duodenal mass was 2.9 cm in diameter and was diagnosed as a neuroendocrine tumor with immunohistochemistry positive for gastrin expression (Figure 1). The hemicolectomy specimen revealed a 4.5 cm,

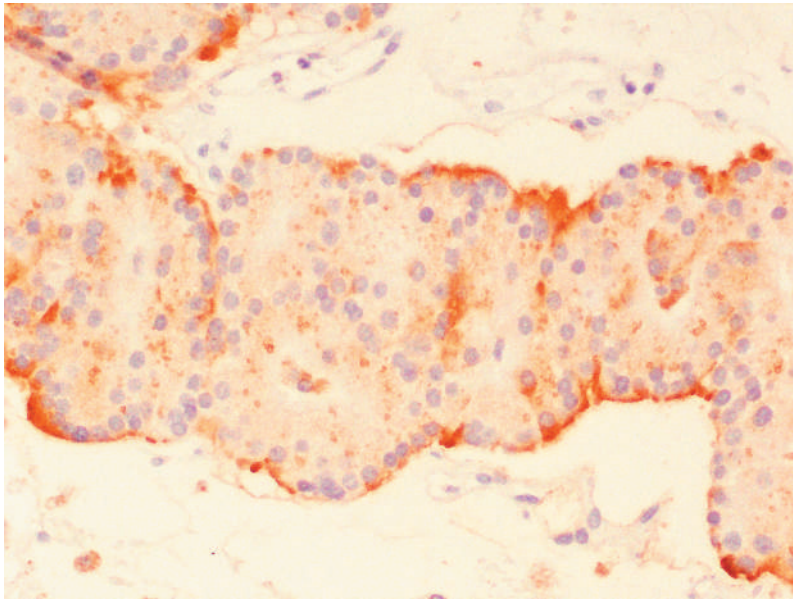
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Received 19 October 2005 Accepted 7 February 2006

www.nature.com/clinicalpractice  
doi:10.1038/ncponc0482



**Figure 1** Gastrin expression by a neuroendocrine tumor of the duodenum. Immunoexpression of gastrin detected by the avidin–biotin complex technique is shown as brown granules in the more-peripheral cells of the neoplastic islands.

#### GLOSSARY

##### ZOLLINGER–ELLISON SYNDROME (ZES)

A rare disorder in which gastrin-secreting tumors in the pancreas and duodenum increase acid production causing ulceration of the stomach and duodenum

poorly differentiated cecal adenocarcinoma. The tumor extended into the subserosal adipose tissue with perineural and extensive lymphovascular invasion. Six of nine lymph nodes showed metastatic adenocarcinoma with a clinicopathologic tumor-node-metastasis classification of stage III (T3N2M0). The right hemicolectomy specimen also demonstrated 22 colonic polyps with various histologic phenotypes. Ten of these polyps exhibited features of sessile serrated adenoma (SSA), and four were mixed polyps (part SSA and part adenoma) of which two had foci of intramucosal carcinoma. The remaining polyps comprised two tubular adenomas, two tubulovillous adenomas, one traditional serrated adenoma and three hyperplastic polyps (HPs).

The patient received leucovorin and 5-fluorouracil chemotherapy from May 1997 to June 1998. Annual follow-up colonoscopies over the next 8 years revealed continued development of at least nine colonic polyps with various histologic appearances (tubular adenomas, tubulovillous adenomas, HPs, and serrated adenomas), each of which was removed by polypectomy. No recurrent or metachronous colorectal carcinoma (CRC) was detected during any of these procedures. There has been no postresection recurrence of gastrinoma or metastasis and at last follow-up, in November

2005, the patient was well with gastrin levels within the normal limits. Subsequent screening for a germline mutation in the multiple endocrine neoplasia type 1 gene (*MEN1*) that encodes menin was negative.

#### DISCUSSION OF DIAGNOSIS

Approximately 75% of gastrinomas occur sporadically; the remainder are associated with *MEN1* syndrome.<sup>1</sup> This syndrome is an autosomal dominant disorder caused by mutations in the *MEN1* gene and occurs in 2 in every 100,000 people. The disorder is characterized by parathyroid hyperplasia and adenomas, resulting in the development of primary hyperparathyroidism and hypercalcemia, pancreatic endocrine tumors, pituitary and adrenal adenomas, as well as an increased incidence of foregut carcinoids, lipomas, and various smooth muscle and skin lesions.<sup>2</sup>

Gastrinomas are also associated with ZES, a rare condition characterized by multiple peptic ulcers in the duodenum and jejunum and with an incidence of 1–3 cases per million people each year. ZES has a slight male predominance (56 males : 44 females) and has a mean age of onset of 41 years. Abdominal pain, diarrhea, and gastroesophageal reflux disease are common presenting symptoms, with abdominal pain and diarrhea seen in approximately 70% of patients. Many patients report these symptoms for approximately 5–6 years prior to the diagnosis of ZES.<sup>1</sup>

HPs of the colorectum have for many years been regarded as non-neoplastic lesions without malignant potential. These polyps are thought to arise through inhibition of apoptosis leading to retention of surface and crypt epithelium, which then adopts a characteristic serrated contour. The underlying genetic changes include mutation of either *BRAF* or *KRAS* oncogenes and the silencing of multiple genes through promoter methylation. HPs have been linked with the subset of colorectal cancer that shows DNA microsatellite instability (MSI) as well as mutation of *BRAF*, and DNA methylation. In this subset, MSI occurs through the methylation and silencing of the DNA mismatch repair gene, *MLH1*. Mutation of *BRAF* and increased DNA methylation are not found in all HPs, but occur most frequently in large HPs that present in the proximal colon.<sup>3</sup> These polyps show exaggerated glandular serration and other atypical features, allowing them to be distinguished histologically from classical, small HPs; these large polyps have been renamed SSAs.<sup>4</sup>

Hyperplastic polyposis (HPP) shows two main phenotypes: multiple, small pancolonic HPPs; and relatively small numbers of large, proximal HPPs, showing the features of SSA.<sup>5</sup> The presentation of the patient in this case study clearly exceeds the criteria for the second phenotype. In this case, methylation-specific polymerase chain reaction was used to analyze DNA methylation of ten markers (MINTs 1, 2 and 31, *p16*, *RASSF1*, *RASSF2*, *NORE1* (also known as *RASSF5*), *MST1*, *CHFR*, and *RKIP*) in seven SSAs, two mixed polyps, the colon carcinoma and the gastrinoma. All polyps showed DNA methylation in at least 7/10 markers. The colon cancer and gastrinoma showed methylation in 10/10 and 7/10 markers, respectively. Interestingly, two samples of entirely normal colonic mucosa also showed extensive DNA methylation. Additionally, the mixed polyps and colon cancer showed methylation and loss of expression of *MLH1* and MSI. All but one polyp and the colon cancer showed mutation of *BRAF*. One mixed polyp had a *KRAS* mutation, while the gastrinoma was negative for both *BRAF* and *KRAS* mutations.

The most intriguing aspect of this case is the presence of concurrent gastrinoma and HPP. Gastrin is associated with proliferation defects and is thought to be involved in adenoma progression within the VOGELSTEIN MODEL of CRC.<sup>6,7</sup> Using methods that quantify all molecular forms of gastrin, progastrin or progastrin-derived peptides have been detected in 80–100% of CRCs.<sup>8</sup> Gastrin might increase proliferation through interactions with its receptor (cholecystokinin B receptor), which activates transcription directly via nuclear translocation of gastrin,<sup>9</sup> or indirectly through pathways dependent on protein kinase C.<sup>10,11</sup> Gastrin might also mediate its trophic effect by upregulation of EGFRs,<sup>12</sup> or by increasing production of mitogens such as the family of regeneration (Reg) proteins, which are known to act on the pancreatic gland and gastric mucosa.<sup>13</sup> Much of the research into gastrin and its relationship with CRC has focused on its role in the traditional adenoma–carcinoma sequence. Since progastrin and gastrins can have anti-apoptotic effects,<sup>14</sup> however, it is possible that progastrin and its derivatives might contribute to the progression of lesions within the serrated neoplasia pathway.

In this case, the rarity of HPP and concurrent gastrinoma suggests that the two disorders are related, but this will need to be confirmed by

additional studies. Genes involved in the pathogenesis of neuroendocrine tumors can be silenced through epigenetic modification, such as DNA methylation. One study has shown that methylation of multiple genes occurs in neuroendocrine tumors and that the frequency of promoter methylation in these genes directly correlates with tumor malignancy, and is an independent predictor of early tumor recurrence and reduced patient survival.<sup>15</sup> Since analysis of the normal colorectal mucosa from this patient revealed a methylation defect, it is possible that this abnormality was responsible for the development of both the gastrinoma and the HPP.

### DIFFERENTIAL DIAGNOSIS

The differential diagnosis for this case includes hereditary nonpolyposis colorectal carcinoma (HNPCC). This patient satisfied few criteria for the diagnosis of HNPCC, namely autosomal dominant inheritance of CRC, onset of CRC before 50 years of age, multiple CRC with predilection for the proximal colon, and extracolonic neoplasms, including carcinomas of the uterus, ovary, small bowel, pancreas, pelviureter, or stomach, sebaceous adenomas, or tumors of the central nervous system.<sup>5</sup> The precursor lesion in HNPCC is the classic adenoma, whereas this patient demonstrated a predominance of SSAs. It is important to identify familial colorectal cancer syndromes in view of the implications for patient follow-up, screening for colonic and extracolonic neoplasms, and genetic counseling for other family members.

### TREATMENT AND MANAGEMENT

Few prospective studies have been performed on patients with HPP, mainly because the entity remains to be fully characterized. One study followed 13 patients prospectively with colonoscopic surveillance at least once every 2 years.<sup>16</sup> Of these patients, 54% developed CRCs during the study period, 71% of which were right-sided. Of note, one patient developed CRC within 3 years of HPP diagnosis, despite annual colonoscopic surveillance. All patients were treated with subtotal colectomy with ileorectal or ileosigmoid anastomosis. Based on these results, the authors recommended close colonoscopic surveillance every 1–2 years.<sup>16</sup> A second study found no instances of colon cancer in 15 patients with HPP during 3 years of follow-up; however, in this patient group, the polyps were mainly located in the distal colon.<sup>17</sup>

### GLOSSARY

#### VOGELSTEIN MODEL

A colon carcinoma development model proposed by Fearon and Vogelstein in which successive gene mutations cause progression of normal colonic mucosa to colorectal adenocarcinoma

**Acknowledgments**

We would like to acknowledge the genetic counselors L Kasprzak and L Palma for their assistance. This study was supported by the Canadian Institutes of Health Research (CIHR), grant No. MOP-67206.

**Competing interests**

The authors declared they have no competing interests.

A study conducted in Portugal examined 14 patients with HPP from 12 different families.<sup>18</sup> CRC was diagnosed at the time of the first colonoscopy in 43% of patients, with 66% of the tumors being right-sided. All patients who underwent surgery at the time of the report were treated by total colectomy and ileorectal anastomosis. Among 17 first-degree relatives who agreed to screening colonoscopy, 59% were found to harbor adenomatous, hyperplastic, or other serrated polyps. Seventy percent of relatives with polyps were aged below 45 years.<sup>18</sup>

Based on these and other studies, it is clear that HPP is a precancerous condition and warrants regular colonoscopic surveillance. Following a diagnosis of colorectal cancer, most patients are treated with total colectomy and ileorectal anastomosis; however, the indications for total colectomy might be less clear when polyps are restricted to the proximal colon. In this case, a right hemicolectomy with ileocolonic anastomosis was performed, followed by close annual colonoscopic surveillance.

Evidence suggests that relatives of patients diagnosed with CRC are at increased risk of colorectal neoplasia. The finding of widespread DNA methylation in normal tissues and the duodenal gastrinoma in the patient in this study suggests a possible genetic predisposition to DNA methylation that could be relevant to an increased risk of extracolonic, as well as colonic, neoplasia. The patient has two children who were offered screening colonoscopy, although this option was declined by both.

The continued development of colorectal polyps in this patient suggests that elevated gastrin levels might not have contributed to their initial development. It is conceivable, however, that gastrin could have promoted the subsequent growth, and even malignant transformation, of polyps, but this hypothesis remains speculative. Despite the presence of unfavorable prognostic features, the patient appears to have been cured of the cecal malignancy. The fact that the tumor showed DNA MSI, which is known to be a good prognostic marker,<sup>19</sup> and was possibly dependent on gastrin-mediated growth signals, could be relevant to the excellent outcome.

**CONCLUSION**

This case is unique with respect to the concurrent presentation of two rare conditions, namely HPP and duodenal gastrinoma. The DNA methylation status of both lesional and normal

tissue revealed an underlying methylation defect, which could be linked to the evolution of both the HPs and the gastrinoma. A trophic effect of gastrin upon the tumorigenic pathway subsequent to the initiation of polyps is plausible and could explain the unexpectedly good outcome following surgery.

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