A Limited Case Series of Duodenal Bulb Carcinoid Tumors and a Perspective on Gastrointestinal Neuroendocrine Tumor Development

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Introduction
Our understanding of carcinoid tumors has evolved since first being described in the late 1800s and again in 1907 at which point the term “carzinoide” was designated by S. Obendorfer.1,2 Initially, these carcinoma-like growths were characterized by their indolent nature and typically asymptomatic presentation. Further studies revealed their ability to secrete biologically active amines and peptides.3 Multiple classification systems have since been described based on embryology,4 size,5 histological differentiation, and proliferation rates.6,7 The World Health Organization (WHO) more frequently uses the term “neuroendocrine tumor” (NET) in place of “carcinoid.”8 NETs are considered a rare occurrence and thought to comprise 0.5% of all malignancies.9 The Surveillance Epidemiology and End Results (SEER) registry has reported an increase in the incidence of NETs from 1.09/100,000 to 5.25/100,000 between 1973 and 2004.10 The increase in incidence correlates with the widespread use of imaging and detection of incidental tumors. Neuroendocrine tumors are predominantly found in the jejunum or ileum.9,10 Duodenal NETs are less frequently encountered with an estimated incidence of 0.19/100,000 (10) and accounting for only 2.8% of all carcinoids in a 5-decade analysis.11 The majority of duodenal NETs are localized to the first and second portions of the duodenum; however, in one study 30% were confined to the duodenal bulb.12,13 The most common presenting symptom in patients with duodenal NETs is abdominal pain, although a minority of patients experience diarrhea.12,14 Thus far, to the authors’ knowledge, there have been no reported cases of duodenal NET with carcinoid syndrome.12,14 The majority of cases are asymptomatic and incidentally identified during routine upper gastrointestinal endoscopy.

We present a case series of four patients who were recently diagnosed with duodenal carcinoid tumor at an academic gastroenterology center. Furthermore, we explore the underlying pathophysiology of neuroendocrine tumors, discuss the histopathology, and up to date treatment options such as endoscopic resection.

Case Report 1
A 65 year-old male presented with a three-year history of epigastric abdominal pain. The abdominal pain worsened upon lying down. There was also a 10-year history of heartburn, which was treated in the past year with proton-pump inhibitors with resolution of symptoms. The patient reported intermittent episodes of diarrhea and hematochezia with no flushing or recent weight loss. There was no family history of colon cancer. A double contrast barium enema revealed multiple diverticula throughout the colon with predominance in the sigmoid. The colonoscopy findings included non-thrombosed external hemorrhoids and diverticulosis. Notable findings on upper endoscopy included a 3-mm sessile polyp with bleeding in the duodenal bulb and a hiatal hernia. Pathological examination of the polyp demonstrated carcinoid tumor cells that stained positive for CD56, synaptophysin, and chromogranin immunostains. Of note, a gastric biopsy showed moderate chronic gastritis with focal active inflammation and moderate mucosal atrophy. Helicobacter pylori-like microorganisms were identified with Giemsa staining; triple therapy with omeprazole, clarithromycin, and amoxicillin was started. Serum chromogranin A levels were elevated at 22.0 ng/mL. The duodenal carcinoid was not detected on computed tomographic imaging with contrast, nor was there any evidence of widespread disease. Endoscopic Mucosal Resection was performed and the pathology report demonstrated no histological evidence of carcinoid tumor post-procedure. The patient is currently at 6 months post diagnosis with follow-up planned at 6 months.

Case Report 2
A 56 year-old male presented with a chief complaint of bright red blood in his stools for two weeks. There was a 10-year history of peptic ulcer disease for which the patient was taking a proton-pump inhibitor for an unknown period of time. There was no family history of gastrointestinal malignancy. Upon further testing, the patient was found to have iron-deficiency anemia and heme-positive stool. The upper endoscopy revealed a nodule in the duodenal bulb, gastritis, and esophageal changes consistent with Barrett’s esophagus. The results from the gastric biopsy revealed superficial mild chronic gastritis, but Helicobacter pylori-like organisms were negative on giemsa stain. The colonoscopy findings included a normal ileum, but showed polyps both in the colon and in the rectum. Pathological examination of the duodenal bulb nodule identified it as an NET in one fragment of the duodenal mucosa. The subsequent staining of the tumors cells revealed diffuse positivity for CD56, focal and weak positivity for synaptophysin and negative staining for chromogranin. Pathological examination of the colon and rectal polyps demonstrated tubular adenoma cells and inflammatory changes with focal ulceration. The patient was initiated on oral iron therapy and conservative management. The

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patient is currently doing well six months after diagnosis.

**Case Report 3**
A 39 year-old female presented with a chief complaint of abdominal pain for an unknown period of time. She had a history of gastritis but no family history of colon cancer. The patient underwent upper endoscopy, which revealed a single one cm nodule in the duodenal bulb (Image A). Complete endoscopic mucosal resection was performed (Image B) and the pathology report revealed histological evidence of a well-differentiated neuroendocrine tumor (Picture 1 and 2). The tumor cells stained positively for synaptophysin and chromogranin confirming the diagnosis of a neuroendocrine tumor (Picture 3). The patient is scheduled for a follow-up upper endoscopy.

**Image A**

*Endoscopic image of single one cm nodule in the duodenal bulb.*

**Picture 1**

*Arrows show nests of tumor cells in submucosa (10x)*

*Pathology picture of endoscopic resection of the duodenal mass show tumor cells in submucosa (arrows in picture 1 and 2).*

**Image B**

*Endoscopic image show complete endoscopic mucosal resection.*

**Picture 2**

*Uniform tumor cells with round nuclei and salt and pepper nuclear chromatin (40x). No necrosis or mitosis seen.*

**Picture 3**

*Tumor cells are positive for chromogranin and synaptophysin (Brown stain).*

*Chromogranin and synaptophysin are 2 markers for neuroendocrine differentiation.*

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Case Report 4
A 65 year-old man presented with a chief complaint of pain upon swallowing for two weeks. The patient stated that his pain began after he was extubated during a recent hospitalization for a non-ST elevation myocardial infarction and coronary artery bypass grafting. Computed tomographic imaging without contrast of the abdomen revealed asymmetric mural thickening in the first portion of the duodenum and cholelithiasis. The upper endoscopy showed diffuse mild inflammation in the gastric fundus, gastric body, and in the gastric antrum consistent for mild gastritis. In addition, there was an incidental finding of a duodenal bulb nodule. The upper endoscopic ultrasound revealed multiple duodenal bulb nodules. Endoscopy mucosal resection was performed and pathological examination showed duodenal mucosa with a focus of submucosal well-differentiated neuroendocrine tumor (Picture 1 & 2). The serum serotonin level was measured to be 74 nmol/l and within normal limits.

Discussion
Despite the rarity of duodenal NETs, increasing reports have allowed further characterization of this entity with regards to typical carcinoid features. NETs which are localized to the gastrointestinal tract manifest in a spectrum of presentations ranging from an absence of symptoms in incidental findings on imaging to the classical manifestation of carcinoid syndrome, bowel obstruction, perforation, intussusception, bowel ischemia, and gastrointestinal bleeding. Studies have suggested that the most common complaints in patients with duodenal NETs are dyspepsia and epigastric pain. Consistent with these studies, our case reports presented patients whom presented with chief complaints and significant histories of dyspepsia and epigastric pain associated with diarrhea. However in these cases, none of the patients reported any symptoms consistent with a flushing sensation.

Histologically, duodenal NETs have been found to display features typical of carcinoid tumors which are pathologically described as monomorphic islands of small cells with round nuclei surrounded by scarce cytoplasm. They are classically diagnosed by measuring 5-hydroxyindoleacetic acid (5-HIAA) excretion in urine. The sensitivity of the 5-HIAA assay is highly variable and is dependent upon whether the tumor is in the foregut, midgut, or hindgut. In a study of 301 carcinoid tumors, only 31% of foregut tumors expressed elevated levels of 5-HIAA. Another study of 24 patients with duodenal NETs was unable to detect any elevated 5-HIAA levels. In contrast, serum chromogranin A has proven to be more reliable in the assessment of neuroendocrine tumors. There is higher percentage of duodenal NETs exhibiting elevated serum chromogranin as compared to duodenal NETs with normal serum chromogranin. It is becoming evident that its value lies primarily in monitoring treatment response and progression to metastatic disease. Upon biopsy of duodenal NETs, immunohistochemical staining shows 75-100% positivity for chromogranin A and 60-100% positivity for synaptophysin. Note worthy from our case reports is the fact that chromogranin A staining was negative in one of our patients.

While the definitive etiology of carcinoid tumor is still unclear, hypergastrinemia may be a pivotal factor in the proliferation of enterochromaffin-like (ECL) cells that undergo dysplasia. This theory has been supported by a histopathological model that follows carcinoid development from ECL cell hyperplasia to dysplasia and furthermore to neoplasia with induced hypergastrinemia. These conditions are achieved by prolonged acid suppression with proton pump inhibitors (PPIs), which in turn have been thought to cause neuroendocrine tumors and carcinomas. Chronic PPI use has been shown to modestly elevate gastrin levels to between 200-400pg/ml in 20-25% of patients, and elevations to 400pg/ml in 1-3.3% of patients infected with H. pylori. In a separate study, ECL cell hyperplasia markedly increased from 2.6% of patients before treatment to 29.2% of patients after 5 years of PPI use. This further supported the role that acid suppression played in the sequence of carcinoid development.

Isolated hypergastrinemia has not been proven to be sufficient for transformation of ECL cells. There is contribution of additional factors such as atrophic gastritis. Indeed, ECL cell dysplasia and carcinoid development have been linked to chronic atrophic gastritis, albeit they are considered a rare occurrence. Furthermore, ECL hyperplasia and a gastric carcinoid tumor have been reported in a patient with normal gastrin levels and with H. pylori infection. Interestingly, patients with profound hypergastrinemia, greater than 400pg/ml, are associated with a higher prevalence of H. pylori infection and atrophic gastritis. The effects of H. pylori induced atrophy of oxyntic mucosa extends to hyperplasia of not only ECL cells, but also proximal gastric parietal cells in the duodenum. Collectively, these studies point to H. pylori infection as a facilitator of carcinoid development.

Herein, we report two case reports of carcinoid tumor occurring in the duodenal bulb, in the context of chronic dyspepsia and concurrent PPI use. Consistent with previous studies, both of the patients exhibited moderate levels of gastritis and atrophy was revealed in the patient who was infected with H. Pylori. Although the prevalence of NETs has increased, whether these findings have significant implications in patients who are chronic PPI users still remains a realm of further investigation.

References
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A Limited Case Series of Duodenal Bulb Carcinoid Tumors and a Perspective on Gastrointestinal Neuroendocrine Tumor Development (Continued)


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