Introduction

Brunner's gland hamartoma (BGH), characterized by benign proliferation of the Brunner's glands, was first described by Cruveilhier in 1835. Since then, case reports have been sporadic, and virtually all were clinicopathologic studies. Many patients with BGH were asymptomatic, while others presented with bleeding, duodenal obstruction, intussusception, or obstruction of the common bile duct or pancreatic duct. These patients were classified as having hamartomas because the proliferation of the Brunner's gland was accompanied with other components, such as smooth muscle bundles and Paneth cells, all of which are native components of this anatomic location. BGHs have not been studied for their possible dynamic aspect either as a target organ or as the primary site of functional alteration, and they remain a clinicopathologic curiosity.

Materials and Methods

We subjected seven duodenal lesions fulfilling the criteria of BGHs to clinicopathologic, histologic, histochemical, and immunohistochemical studies. Clinically, four patients had gastric ulcers, one had renal failure, one had both renal failure and chronic pancreatitis, and one had heart disease. Seven BGHs that were surgically removed and 12 duodenal biopsies with endoscopically and histologically normal Brunner's gland (NBG) were collected for this study. The nodular lesions classified as BGHs were single, located in the first portion of the duodenum (including the pyloroduodenal junction), and measured greater than 5 mm in size. The important clinical features of each patient's medical record are summarized in Table 1. Sections were stained with hematoxylin and eosin, mucicarmine, and Alcian blue (pH 1.0 and 2.5).

Periodic acid-Schiff (PAS) with and without diastase digestion.

<table>
<thead>
<tr>
<th>Case</th>
<th>Patient Age</th>
<th>Sex</th>
<th>Presenting Symptom</th>
<th>Other Diseases</th>
<th>Endoscopic Findings</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>77</td>
<td>M</td>
<td>Hematemesis, melena</td>
<td>Gastrointestinal bleed, hiatal hernia</td>
<td>1.0 cm polypoid mass in the second portion of duodenum</td>
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<tr>
<td>2</td>
<td>91</td>
<td>M</td>
<td>Hematemesis, melena</td>
<td>Chronic pancreatitis, chronic renal failure</td>
<td>1.2 cm synchondromatous mass in the second portion of duodenum</td>
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<tr>
<td>3</td>
<td>57</td>
<td>M</td>
<td>Hematemesis</td>
<td>Gastric ulcer</td>
<td>Gastric ulcer, 0.9 cm polypoid mass in the duodenal bulb</td>
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<tr>
<td>4</td>
<td>81</td>
<td>M</td>
<td>Nausea, hematemesis</td>
<td>Gastric ulcer, diabetes mellitus, hypertension</td>
<td>0.9 cm polypoid mass forming the pylorus</td>
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<tr>
<td>5</td>
<td>92</td>
<td>F</td>
<td>Epigastric discomfort</td>
<td>End-stage renal disease, diabetes mellitus, hypertension</td>
<td>0.9 cm polypoid mass in duodenal bulb</td>
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<tr>
<td>6</td>
<td>87</td>
<td>F</td>
<td>Hematemesis</td>
<td>Gastric ulcer</td>
<td>0.9 cm polypoid mass in duodenal bulb, gastric ulcer</td>
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<tr>
<td>7</td>
<td>41</td>
<td>M</td>
<td>Syncope, emesis, melena, abdominal pain, vomiting</td>
<td>Gastric ulcer</td>
<td>Gastric ulcer, 1.0 cm polypoid mass forming the pyloroduodenal junction</td>
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*All presented with anemia and upper gastrointestinal hemorrhage.*

For immunohistochemical study, the standard avidin-biotin complex method was used. Deparaffinized sections (4 μm in thickness) were cut and stained for the following markers: pepsinogen II (PG II) - 1:1,000, carcinoembryonic antigen - 1:1,000 (Dako Corp, Santa Barbara, Calif), chromogranin - 1:400 (Biogenex, San Ramon, Calif), serotonin - 1:5 (Dako Corp), somatostatin - 1:5 (Dako Corp), and gastrin - 1:75 (Dako Corp). Table 2 presents the results of the immunohistochemical stains and the semiquantitative criteria used to analyze the stained slides.

<table>
<thead>
<tr>
<th>Case</th>
<th>Chromogranin</th>
<th>CEA</th>
<th>Gastrin</th>
<th>PG II</th>
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Results

Of the seven patients, five were men and two were women, and their ages ranged from 39 to 77 years. All patients presented with anemia and upper gastrointestinal hemorrhage. All but one of the BGHs were located in the first portion of the duodenum, and the seventh was located in the pyloroduodenal junction. Four patients (cases 3, 4, 6, and 7) also had gastric ulcers. Their upper gastrointestinal hemorrhage was probably due to the bleeding gastric ulcers, and their BGHs were incidental findings. The BGHs in cases 3, 4, and 6 were found during surgery for the gastric ulcers, and case 7 had a partial gastrectomy. Because of the previously reported association of BGH and gastric ulcer,\(^3,12,13\) the specimen was serially sectioned and a nodular lesion was found in the pyloroduodenal junction. Histologically, this lesion was a BGH. Two patients had a history of renal failure (cases 2 and 5), one of whom also had a history of chronic pancreatitis (case 2). Case 1 had a history of old myocardial infarction and chronic heart failure but no history of ulcer, renal failure, or pancreatitis.

Grossly, all seven BGHs were nonencapsulated but well-circumscribed nodules of white, pink, or tan tissue and ranged from 0.6 to 1.8 cm in greatest dimension. Microscopically, the seven BGHs were similar, although there were minor architectural differences. The cells were arranged in a lobulated fashion and were compartmentalized by fibromuscular septa. Cystic dilatation of the glands was observed in three lesions (Fig 1). The individual cells were columnar with vacuolated cytoplasm and basally located nuclei and basically similar to those of NBG. The proliferative process took place in the submucosal zone. Histochemically, both the Alcian blue and the mucicarmine stains were negative except for occasional cells with a trace of staining. The PAS stain (with and without digestion) was positive in BGH and in NBG.

In cases 1, 3, and 7, the hamartomas showed more intense and diffuse PG II immunoreactivity (Fig 2). Although diffusely positive, the intensity of PG II stain in the individual cells was weak in case 2, and the PG II stain was negative in case 4. Comparable to NBG, the PG II immunoreactivity in cases 5 and 6 was weak to moderate and focal. Chromogranin-positive cells were found in five cases (2, 3, 4, 5, and 7). Serotonin positivity was identified in all but case 2. Immunoreactivity for somatostatin and gastrin was identified in all cases. When present, the immunoreactive cells were observed either singly or, more often, in clusters (Fig 3). Clusters of carcinoembryonic antigen immunoreactive cells were identified only in cases 1 and 7. The NBGs were negative for chromogranin, somatostatin, serotonin, and gastrin.

Discussion

The BGHs in this study are so designated because they are composed of Brunner's glands (similar or identical to their normal counterparts) and fibromuscular septa, both of which are normal components of the duodenum. Though not identified in the NBG in this study, endocrine cells have been demonstrated in the Brunner's gland by electron microscopy\(^16\) and by immunofluorescence technique.\(^17\) The endocrine cells displayed in our BGHs were proliferative as reflected by their clustering appearance. Nodular proliferation of these native components as seen in the seven cases of BGH, therefore, fulfills the conventional definition of a hamartoma, ie, abnormal growth of mature normal cells and tissues in an organ composed of identical elements.\(^18\) These elements seen in the BGH are thus analogous to those in other types of hamartomas (eg, bronchial hamartoma). However, when the clinical features and the immunohistochemical results in these BGHs are scrutinized, a strong possibility is raised that BGH may represent a form of localized functional hyperplasia.
Besides its cytologic similarity to the normal Brunner's gland, BGHs are virtually indistinguishable from the Brunner's gland hyperplasia by light microscopic examination. This similarity has led us to review the clinical settings in which Brunner's gland hyperplasia occurs. If the similarity extends to the clinical aspect, the pathophysiological explanations for hyperplasia may also be applied to hamartoma.

Stolte et al. studied 105 duodenopancreatectomy specimens and found that 75.5% of the cases of pancreatitis had associated diffuse Brunner's gland hyperplasia as confirmed by histologic examination with measurement of the Brunner's glands. They speculated that the hyperplasia may be an adaptive reaction to either the exocrine insufficiency of the inflamed pancreas or the changes in gastric function caused by pancreatitis, or it may develop simultaneously as a result of gastrointestinal hormonal disturbances. One of our patients (case 2) had a history of pancreatitis but also suffered from renal failure.

In patients with chronic renal failure, approximately 15% have Brunner's gland hyperplasia. In a study of 15 patients with renal failure, five had multiple polypoid hyperplasia, both macroscopically and microscopically, another five had microscopic evidence of Brunner's gland hyperplasia, and the remaining five had no such association. The mean serum PG II was elevated in patients with severe or mild hyperplasia, which was attributed to the Brunner's gland hyperplasia. Two of our patients had renal failure. Although serum PG II analysis was not performed, the immunoperoxidase stain showed an increase in stable PG II in one of the two cases (case 2).

It is well known that the PG II is threefold higher in patients with duodenal ulcer than gastric ulcer but the PG II is higher in patients with gastric ulcer than duodenal ulcer. The source of the serum PG II was not determined. The chief cells of the stomach, the Brunner's glands, and even the prostatic glands are known to secrete PG. Recent studies of the surgically resected specimens for duodenal ulcers revealed Brunner's gland hyperplasia in these specimens, especially near the ulcer. These findings are similar to those in animal experiments in which marked proliferative activity of the Brunner's glands was found, as measured by [3H]-thymidine autoradiography. The authors speculated that the hyperplastic Brunner's glands in these surgically resected specimens serve as a duodenal mucosal defense factor against the acid-peptic digestion since patients with duodenal ulcers who require surgical treatment usually show gastric hyperacidity. Although none of our seven patients had a duodenal ulcer, four had associated gastric peptic ulcers. These patients probably had low acid levels. The retrospective nature of this study, however, does not allow us to study the gastric acidity or possible pathogenetic relationship between the gastric ulcer and Brunner's gland proliferation. The high association strongly suggests some significant cause/effect relationship rather than a chance occurrence and therefore warrants further investigation.

It is conceivable that endocrine cells could be identified in the proliferative Brunner's glands since endocrine cells can be identified in the normal Brunner's glands by electron microscopy and immunofluorescence technique. However, the unexpected increase in endocrine cells suggests that the etiologic factors for the Brunner's gland proliferation also act on the endocrine component or that the stimuli trigger the precursors that then undergo dual proliferations. We found a single case report of a BGH in which a microcarcinoid was described. The endocrine cells in the BGHs under study stained for the universal endocrine cell markers (chromogranins, neuron-specific enolase, and specifically somatostatin and gastrin).

Despite their histologic and cytologic features that fulfill the conventional definition of hamartoma, these BGHs demonstrate a high association with other diseases similar to that seen in diffuse hyperplasia. The increase in stainable PG II in some cases and the increase in endocrine cells suggest that BGH may represent cases of localized functional hyperplasia rather than developmental phenomena.

We found no reports in the current English literature dealing with either management or prognostic differences between BGH and hyperplasia.

The antiserum to PG II was kindly provided by I. M. Samloff, MD, of the Veterans Administration Medical Center, Sepulveda, Calif.

References