features have been reported in the literature.[8] Lesions less than 5 cm in size may be amenable to endoscopic or laparoscopic excision.[12] CT or MRI does not distinguish a Brunner gland hamartoma from other duodenal tumors but may define its relationship to other structures such as the pyloric channel, gastric antrum, ampulla of Vater, or pancreatic head. The differential diagnosis of smooth-walled duodenal filling defects includes leiomyomas, gastrointestinal stromal tumors, lipomas, neurogenic tumors, carcinoid tumors, hamartomas, aberrant pancreas, prolapsed pyloric mucosa, or Peutz-Jeghers polyps.[5]

In summary, Brunner gland hyperplasia is a common finding on upper endoscopy. However, hamartomas are rare and, when accompanied by bleeding or obstruction, commonly require endoscopic or surgical resection. Brunner hamartomas can become giant-sized, resulting in gastroduodenal intussusception and gastric outlet obstruction. These tumors are polypoid, typically bulbar, often pedunculated, and can be quite vascular. Endoscopic surveillance is not required due to extremely infrequent malignant degeneration and no evidence of recurrence following endoscopic or surgical excision.

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Review

Brunner Gland Hamartoma

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Brunner glands are branched acinotubular glands in the submucosa of the duodenum. They are located mainly in the duodenal bulb, proximal duodenum, and, with a progressive decrease in number and size, in the distal duodenum. Embryologically, these glands develop in humans during the thirteenth and fourteenth weeks of gestation.[1] With age, they constitute a smaller portion of the duodenal area, from an estimated 55% in infancy to 35% at 50 years of age.[2] First described by Brunner in 1688, these glands were originally thought to be "pancreas secundarium." However, in 1846, Middeldorp identified these submucosal duodenal glands as a separate entity.[3]

The Brunner glands, which empty into the crypts of Lieberkuhn, secrete an alkaline fluid composed of mucin, which exerts a physiologic anti-acid function by coating the duodenal epithelium, therefore protecting it from the acid chyme of the stomach. Furthermore, in response to the presence of acid in the duodenum, these glands secrete pepsinogen and urogastrone, which inhibit gastric acid secretion.[1]

In the past, there has been significant debate regarding the nomenclature of Brunner gland proliferation. Cruveilhier, in 1835, and Savioli, in 1876, described the first cases of "adenoma" of the Brunner gland.[4] In 1934, Feyrter categorized the abnormal proliferation of Brunner glands into the following types: type 1, diffuse nodular hyperplasia, in which multiple sessile projections are found throughout the duodenum; type 2, circumscribed nodular hyperplasia, in which sessile projections are limited to the duodenal bulb; and type 3, glandular adenoma, in which there are polypoid tumor-like projections.[4] It remains a matter of debate whether these three presentations are the result of the same pathologic process.

Hyperplasia of Brunner glands with a lesion greater than 1 cm was initially described as a Brunner gland adenoma.[5] Several features of these lesions favor their des-

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ignation as hamartomas, including the lack of encapsulation; the mixture of acini, smooth muscles, adipose tissue, Paneth cells, and mucosal glands; and the lack of any cell atypia.[4] These hamartomas are rare, with approximately 150 cases described in the literature.[6] It is estimated that they represent approximately 5–10% of benign duodenal tumors. They are variable in size, typically 1–3 cm, with only a few reported cases of lesions larger than 5 cm. Brunner gland hamartomas appear pedunculated in the majority of cases.[7] The lesions must be differentiated from adenomas, leiomyomas, lipomas, neurogenic tumors, leiomyosarcomas, aberrant pancreatic tissue, prolapsed pyloric mucosa, and cystic dystrophy of the duodenal wall. Most cases have been reported in patients between the ages of 40 and 60 years, with no gender predominance, though cases have been described from early infancy to 80 years of age.[6]

The pathogenesis of Brunner gland hamartoma remains unclear. Because of the anti-acid function of Brunner glands, it has been postulated that hyperchlorhydria could stimulate these structures to undergo hyperplasia.[4] In one study, 45% of patients with Brunner gland hyperplasia had increased gastric output; however, 20% of these patients were reported to have gastric hypoacidity.[8] Franzin and colleagues reported an association between these lesions and hyperchlorhydria in patients with chronic gastric erosions and duodenal ulcers; however, other studies have not confirmed these findings.[9] Spellberg and associates did not find evidence of regression of Brunner gland hyperplasia after acid suppressive therapy with H2-receptor blockade.[10] It has been suggested that *Helicobacter pylori* infection may play a role in the pathogenesis of Brunner gland hamartomas. In a study involving 19,100 subjects, Kovacević and coworkers found that 5 of 7 patients diagnosed with these hamartomas had concurrent *H. pylori* infection.[11] A pathogenic link, however, is difficult to draw given the rarity of these lesions and the high prevalence of *H. pylori* in the general population. Another theory is that these hamartomas may form as a hyperplastic reaction to inflammation, given the inflammatory cell infiltrate (typically lymphocytes) occasionally witnessed histologically. Supporting evidence for this assertion is insufficient given that the presence of lymphocytes is not unusual in normal submucosa throughout the gastrointestinal tract.[5] Associations of Brunner gland hyperplasia have also been reported with uremia and chronic pancreatitis. In one large series, diffuse hyperplasia of Brunner glands was seen in 76% of patients with chronic pancreatitis who underwent pancreaticoduodenectomy, raising the question of whether this represents an adaptation to pancreatic exocrine insufficiency.[12]

Most patients with Brunner gland hamartomas are asymptomatic or have nonspecific complaints such as nausea, bloating, or vague abdominal pain.[2,13] In these cases, the lesion is usually an incidental finding detected during esophagogastroduodenoscopy or imaging studies. The most common presentations in symptomatic patients are gastrointestinal bleeding (37%) and obstructive symptoms (37%).[7] In a review of 27 cases of Brunner gland hamartoma from 1914 to 1993, Levine and colleagues found that the majority of patients with tumor-related blood loss had melena and showed evidence of chronic bleeding with ulceration of the majority of these tumors. Lesions beyond the first portion of the duodenum had a higher tendency to bleed, possibly due to more stress and vascular compromise from gastrointestinal motility than lesions in the first portion of the duodenum. Patients who presented with obstructive symptoms tended to be symptomatic for a longer period of time before diagnosis (median, 30 days of symptoms). Although asymptomatic patients had smaller lesions (mean, 1.6 cm), patients with obstructive and bleeding symptoms had similar-sized lesions (mean, 2.1 and 2.8 cm, respectively).[7] Involvement of the ampulla of Vater has been associated with uncommon manifestations, including obstructive jaundice, biliary fistula, and recurrent pancreatitis.[1,14] On rare occasions, patients can present with gastric outlet obstruction due to circumferential hyperplasia or a duodenal polyp. Obstructive symptoms caused by intussusception, as presented in the case reported by Petersen and associates, is rare, with only a few reported cases.[15,16] The case presented by Petersen and coworkers is therefore an unusual presentation of a rare lesion.

Diagnosis is usually confirmed by the use of imaging studies and upper endoscopy. Smooth-walled polypoid filling defects may be seen in the duodenal bulb or corresponding portion of the duodenum on upper gastrointestinal barium studies.[3] Endoscopy localizes the lesion; however, biopsies are usually negative or reveal only Brunner gland hyperplasia due to the submucosal nature of the tumor.[17] Computed tomography is useful to confirm the absence of extraluminal extension of the lesion as well as to delineate its relationship to the pancreas, common bile duct, and vasculature.[1] Endoscopic ultrasound (EUS) is helpful in assessing the origin, extent, and vascularity of these suspected submucosal lesions. Hizawa and coworkers described EUS features seen on 6 cases of Brunner gland hamartoma, which were of a heterogeneous solid or cystic mass within the submucosa.[18]

Although Brunner gland hamartoma is not considered premalignant, there have been very rare reports of focal cellular atypia within the lesion. Fujimaki and colleagues reported sporadic immunopositivity for p53 in a focus of atypical glands within a Brunner gland hamartoma.[19] There has also been a case reported of two microcarcinoid foci seen in a pedunculated Brunner gland hamartoma in an asymptomatic patient.[20] More recently, Suda and

associates reported a case of a duodenal polyp consisting of Brunner-like glands, with evidence of histologic transition within the polyp from hyperplastic to adenomatous areas.[21] This finding raises some concern for the presence of a "true" Brunner gland adenoma. Adenocarcinoma within the duodenum has also been reported, on rare occasions, arising from an area of Brunner gland hyperplasia, which on previous endoscopic biopsies demonstrated benign-appearing glands.[17] These reports are exceedingly rare and with unclear clinical relevance. Therefore, conservative treatment with endoscopic polypectomy or limited surgical resection is appropriate. Removal of the suspected Brunner gland hamartoma is recommended to both confirm the diagnosis as well as to avoid potential complications, including obstruction and bleeding.

Most reports in the literature describe local surgical resection of Brunner gland hamartoma via duodenotomy. Increasingly, successful endoscopic resection has been reported and is primarily used for pedunculated Brunner gland hamartomas. The endoscopic approach in selective cases appears to be safe, less invasive, and less costly.[17] The size of the endoscopically resected lesions has ranged from 0.5 cm to more than 5 cm.[22] The precise localization of hamartomas distal to the duodenal bulb is imperative to avoid inadvertent thermal trauma to the ampulla of Vater and therefore the risk of acute pancreatitis.[17] On rare occasions, extensive surgical resection such as pancreatoduodenectomy may be performed when the lesion is large and malignancy is suspected.[1,23] The long-term outcome after Brunner gland hamartoma resection is favorable, without any reported recurrences of lesions or local development of gastrointestinal neoplasm.[7]

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