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# Duodenal Stricture Caused by Concomitant Immunoglobulin G-4 (IgG-4) Related Disease and Brunner's Gland Hamartoma

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## Abstract

Benign duodenal tumors are less common than their malignant counterparts. When it comes to duodenal mass or wall thickening causing obstruction, we tend to view it as malignancy. In the following sections, we describe a 40-year-old man who underwent surgical resection due to duodenal stricture. Contrary to common beliefs, histopathology examination revealed concurrent duodenal immunoglobulin G-4 related disease (IgG4-RD) and Brunner's gland hamartoma (BGH).

**Key Words: IgG4 related disease, duodenal tumor, Brunner's gland hamartoma, duodenal obstruction**

## Introduction

Most duodenal tumors are malignant[1]. In this article, we give an account of a 40-year-old man with a giant obstructive duodenal mass caused by concomitant IgG4-RD and BGH. Meanwhile, a comprehensive review on relevant medical literature and explanations for this novel finding will also be provided.

## Case report

A 40-year-old man who had been healthy previously presented with long-standing epigastric pain. On initial encounter, abdominal sonography showed wall thickening over the proximal duodenum (Figure 1). The laboratory data were unremarkable except for a slightly elevated lipase level (110 IU/L; reference range < 60). Due to above image

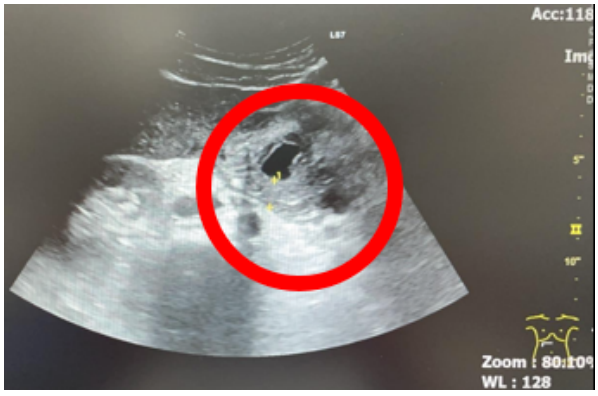


Figure 1. Abdominal sonography showing wall thickening over the proximal duodenum (red circle).

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finding, we suggested endoscopic study for this lesion. However, he refused our advice and lost follow-up during the following one year.

Owing to progressively aggravating epigastric pain combined with new onset vomiting, poor intake, and body weight loss more than 10 kilograms over a 6-month interval, he visited our hospital again and requested esophagogastroduodenoscopy (EGD). The regular size endoscopy was able to reach the ampulla of Vater and revealed a giant circumferential mass at least 5cm in size extending from distal bulb to the second portion of the duodenum proximal to ampulla, causing luminal stenosis without food residue (Figure 2). Under the impression of duodenal malignancy, we performed endoscopic biopsy over the mass lesion. However, the result showed only non-specific chronic inflammation and hyperplastic polyp. Therefore, he underwent contrast-enhanced abdominal computed tomography (CT) where a giant lesion 7cm in diameter with concentric wall thickening at the first and second portion of the duodenum was found (Figure 3). To better characterize surrounding pancreaticobiliary structures, magnetic resonance cholangiopancreatography (MRCP) was performed and didn't show remarkable biliary or pancreatic duct dilatation. Furthermore, there was no obvious invasion of other organ or lymphadenopathy. Compared

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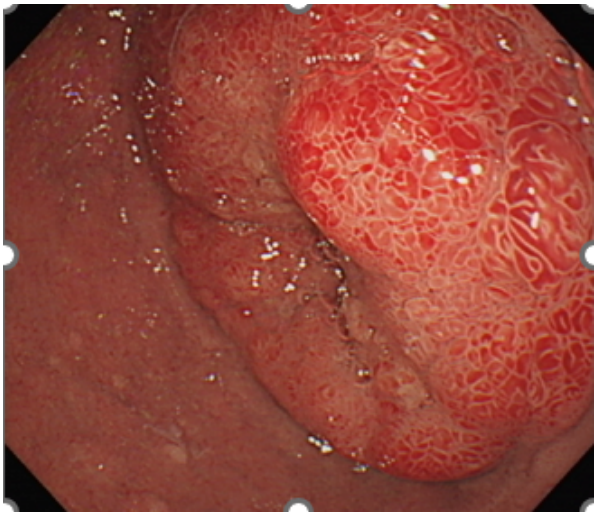

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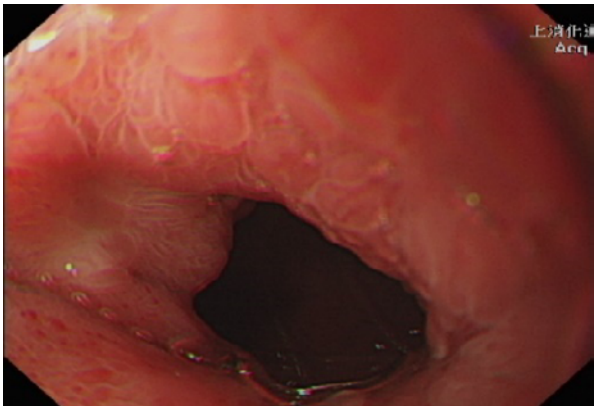


Figure 2. (a)Esophagogastroduodenoscopy revealing a huge duodenal space-occupying lesion causing severe obstruction extending from distal bulb to the second portion proximal to the ampulla Vater. (b)Close-up view showing partial stenosis at the junction of the first and second portion of duodenum.

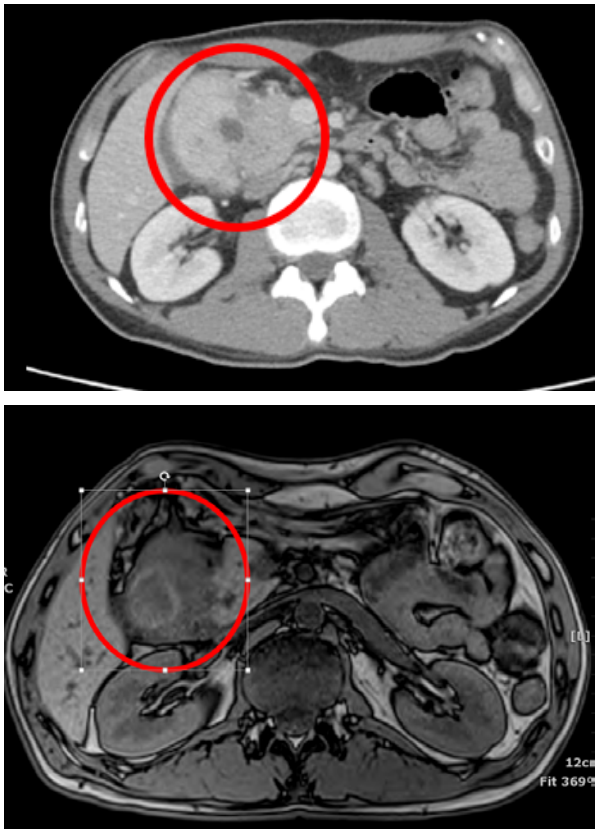
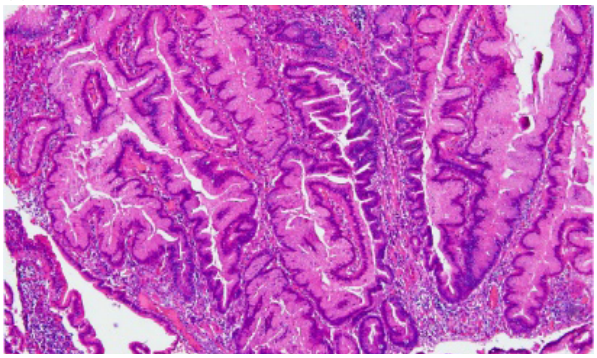


Figure 3. Contrast enhanced abdominal computed tomography (CT) and magnetic resonance cholangiopancreatography (MRCP) of the abdomen demonstrating concentric wall thickening over the proximal duodenum (red circles).

with the laboratory data collected one year ago, an increase in lipase level was detected (from 110 to 331 IU/L). Though other laboratory data, including complete blood count, liver function, urinalysis, or tumor markers, were all within normal limits, surgical management was indicated due to bowel obstruction. Besides, the patient refused endoscopic ultrasonography (EUS) for detailed evaluation of the mass lesion and wished curative treatment. As a result, we performed pancreaticoduodenectomy (Whipple's operation). Duodenal tissues disclosed nodular hyperplasia of Brunner's glands 5cm in size without ulcerations (Figure 4a). Upon further immunohistochemical (IHC) staining, we discovered abundant immunoglobulin G-4 (IgG-4) positive plasma cells (>50 per high power field) with an IgG4 to IgG ratio more than 40% (Figure 4b) adjacent to the aforementioned nodular hyperplasia. Other histopathologic findings included chronic inflammatory cell infiltration in the lamina propria, obliterative phlebitis, and eosinophilia (Figure 4c). Pancreatic pathology revealed necrotizing pancreatitis, possibly attributable to the patient's smoking habit, while regional lymph nodes showed reactive hyperplasia. All the section margin was free from malignancy.

(a)



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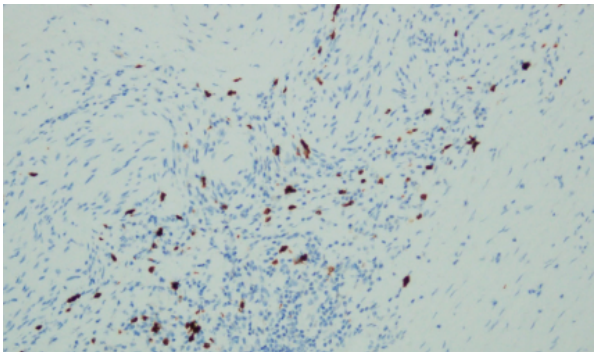

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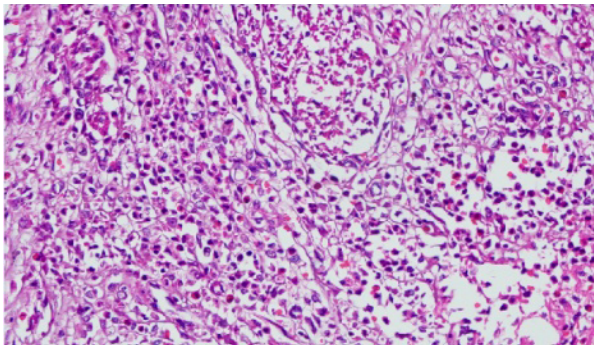

Figure 4. (a) Microscopic appearance of Brunner's gland hyperplasia (Hemotoxylin-eosin stain, 20x). (b) IHC staining disclosing abundant immunoglobulin G-4 (IgG-4) positive plasma cells (>50 per high power field) with an IgG-4 to IgG ratio of more than 40%. (c) Microscopic appearance showing storiform fibrosis, obliterative phlebitis, and eosinophilia (stained by H&E).

Under the impression of coexisting Brunner's gland hamartoma (BGH) and IgG4-related disease (IgG4-RD), additional studies including serum IgG4 level, anti-nuclear antibody (ANA), rheumatoid factor (RF), complement 3/4 (C3/C4) levels, thyroid function test, chest CT, brain magnetic resonance imaging (MRI), and colonoscopy were carried out. Except for a mildly elevated serum IgG4 level (168 mg/dL; reference range < 135), the above investigations were all within normal limit. Tracing back, he denied symptoms which may be related to autoimmunity such as fever, skin rash, joint pain, dry eyes, or dry mouth.

The patient experienced an uneventful postoperative course and recovered well without any complications. He didn't receive medication because of reduced pain and improved appetite. So far, the serum IgG4 level was within normal limit (88 mg/dL).

## Discussion

IgG4-RD is an immune mediated fibrotic

disease following an insidiously progressive clinical course typified by tumor-like mass formation in the affected organs[2]. Being underestimated in clinical practice with unknown prevalence, IgG4-RD can influence any organ in the body, encompassing pancreas, bile ducts, salivary glands, lacrimal glands, kidneys, retroperitoneum, and lungs[3]. Although the underlying mechanism is still poorly understood, evidence suggests that B and T cells play an important role in its pathogenesis[4].

According to the latest guideline, the diagnosis of IgG4-RD is established when there is localized or diffuse swelling or mass in single or multiple organs with elevated serum IgG4 levels combined with infiltration of IgG4 positive plasma cells and lymphocytes, as well as storiform fibrosis and obliterative phlebitis[5]. Further evidence supporting a diagnosis of IgG4-RD is IHC staining illustrating > 50 IgG4 positive cells per high power field (HPF) with an IgG4/ IgG > 40%[6]. Classically, serum IgG4 levels are elevated in IgG4-RD; however, a large portion of patients are found to have normal serum IgG4 levels[7]. In addition, elevated serum IgG4 levels is not specific to IgG4-RD because many conditions could evoke rises in IgG4 levels, including infectious disease or inflammatory bowel disease (IBD)[8]. Therefore, it is difficult to diagnose IgG4-RD based soley on elevated serum IgG4 level. In the workup for IgG4-RD, it is crucial to consider differential diagnoses such as malignancy, autoimmune disorder, sarcoidosis, or connective tissue disease before reaching a definitive diagnosis[9]. In our case, serum IgG4 level may be underestimated because it is measured post-operatively.

Gastrointestinal IgG4-RD is very rare, with few reported cases of intestinal obstruction[10]. Some cases of duodenal IgG4-RD are associated with a history of duodenal ulcers[11]. Under endoscopy, IgG4-related GI disease can present with ulcers, polyps, submucosal tumor, or thick gastric folds[12]. Because the IgG4 positive plasma cells may spread predominantly in the submucosal or even sub-serosal layers[13], it is especially difficult to acquire the correct diagnosis before surgery based on endoscopic biopsy alone. In summary, the rarity of this condition and resemblance to malignancy often necessitate surgical resection to diagnose and treat IgG4-RD[14].

On the other hand, Brunner's glands are found primarily in the deep mucosal and submucosal layers of the proximal duodenum[15]. With an estimated incidence of less than 0.01%[16], BGH typically appears in those 50 to 70 years of age and has no gender predilection[17]. It is believed that mucosal damage from duodenal ulcer, erosions, or foveolar metaplasia may induce proliferation of Brunner's gland[18]. BGHs are virtually benign in most cases, with very few reports showcasing dysplasia or malignant transformation[19]. In previous case reports, association with neuroendocrine carcinoma (NEC), dysplasia, adenocarcinoma, or Giardiasis have been delineated[20-22]. Due to concern about occult malignant degeneration with large BGHs, it may be treated with pancreaticoduodenectomy[23]. How malignant transformation takes place remains to be illuminated. Features portending a cancerous lesion include sessile polyp with central depression, high mitotic activity, or positive p53 expression[24]. Resection, either through endoscopy or surgery, is the only method to cure the disease. Some experts advocate intra-operative frozen section to modify the magnitude of surgery, however, uncertainty about the risk of malignancy makes this approach less favorable[25].

Up until now, the connection between IgG4-RD and BGH has not been proven, and their coexistence may be a coincidence. As far as we know, a common denominator to both conditions is a history of duodenal ulcer. It may be inferred that IgG4 saturated plasma cells could cause mucosal damage with subsequent multiplication of Brunner's glands in a fashion awaiting elucidation. However, the above

conjecture might not be applicable to our case due to a lack of obvious ulcerative lesion.

Duodenal mass lesions are not always synonymous with malignancy; the rarity of duodenal BGH and IgG4-RD poses great challenges to physicians when trying to make an accurate diagnosis. Therefore, comprehensive evaluation of laboratory data, advanced image findings, and immunohistochemistry results should be undertaken in those with concentric duodenal wall thickening or stenosis. More research is warranted to establish the link between IgG4-RD and BGH.

## Conclusion

To the best of our knowledge, this is the first report of duodenal obstruction caused by synchronous BGH and IgG4-RD. In the future, it is reasonable to take IgG4-RD into consideration in the differential diagnosis of any circumflex mass, swelling, or mural thickening in the GI tract.

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# 同時存在的 IgG4 相關疾病及布納氏腺瘤所導致的十二指腸狹窄

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## 摘 要

良性十二指腸腫瘤很少見，造成十二指腸壁增厚、狹窄、或阻塞的時候，常將十二指腸腫瘤視為癌症。本文要介紹一位 40 歲男性，因十二指腸狹窄而接受手術切除，卻發現與一般看法相反的良性腫瘤，病理切片診斷為同時存在的 IgG4 相關疾病及布納氏腺瘤。