



Case Report

A Case of Serotonergic Gastric Neuroendocrine Tumor with Fibrous Stroma an Unusual EUS Finding

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Abstract

Our patient was a man in his eighties who was referred to our department after a screening endoscopy indicated some abnormalities. Upper gastrointestinal endoscopy identified a 6-mm submucosal tumor in the posterior wall of the lesser curvature of the upper gastric body. Endoscopic ultrasonography (EUS) revealed a hypoechoic mass with internal heterogeneity and a heterogeneous shape, mainly situated in the second and third layers of the gastric wall. Following EUS-guided fine-needle aspiration biopsy, the patient was diagnosed with a gastric neuroendocrine tumor (NET) G1. Blood tests showed that he was negative for parietal cell and intrinsic factor antibodies; additionally, the serum gastrin level was normal. Computed tomography did not show metastatic lesions. The patient was diagnosed with a Type III Rindi classification gastric NET. However, the patient was elderly and did not wish to undergo surgery; therefore, endoscopic submucosal dissection was performed. The results of pathological examination confirmed a NET G2, T1b2 (2,000 μ m). Due to prominent fibrous stroma in the tumor, we stained the specimen for serotonin and found that some of the cells were serotonin-positive. Despite further surgical resection, no lesions were found in the dissected lymph nodes or resected gastric tissue. The patient remains recurrence-free 36 months postoperatively. This is a very valuable case as there have not been any reports of a serotonergic gastric NET with fibrous stroma thus far.

Keywords: Endoscopic Ultrasonography, Fibrous Stroma, Gastric Neuroendocrine Tumor, Serotonergic Tumor.

Introduction

A gastric neuroendocrine tumor (NET) is rare, accounting for only 0.6 to 2% of all gastric tumors [1]. In general, the intratumoral parenchyma uniformly consists of tumor cells, and it is believed that fibrosis does not occur inside the tumor. In recent years, pancreatic NET cases have been reported, wherein serotonin produced by the tumor induces fibrous stroma formation inside the tumor. This leads to fibrosis within the tumor [2]. Here, we report a case of a Rindi Type III serotonergic gastric NET that exhibited curious endoscopic ultrasonography (EUS) finding. To the best of our knowledge, there are no other reports on serotonergic gastric NETs. Serotonin production induced formation of fibrous stroma inside the tumor and led to unusual EUS finding. We hereby report this case along with a literature review.

Case Report

Our patient was a man in his eighties who was referred to our department after a screening endoscopy indicated some abnormalities. Upper gastrointestinal (GI) endoscopy revealed a 6-mm submucosal tumor in the posterior wall of the lesser curvature of the upper gastric body. A very slightly depressed erosion was observed at the apex see in (Figure 1).

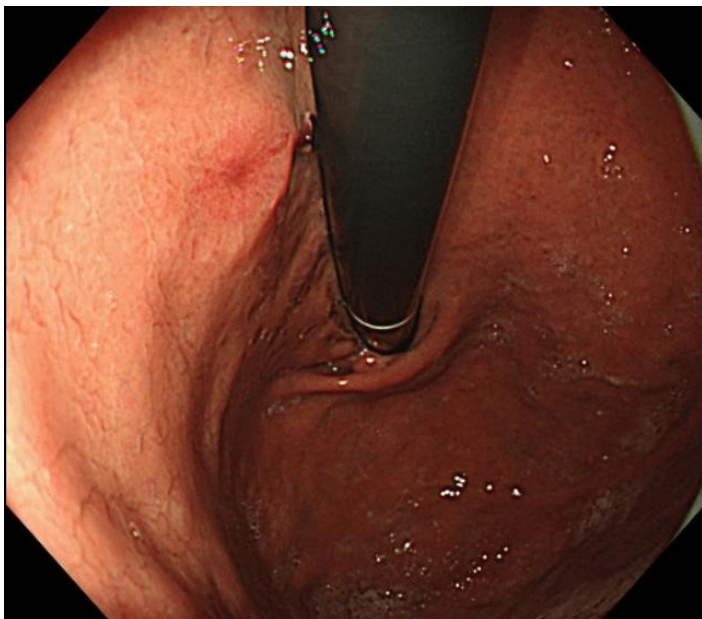


Figure 1: Upper gastrointestinal (GI) endoscopy. A submucosal tumor-like flat protrusion with a central depression is observed on the posterior wall of the lesser curvature of the upper gastric body.

Magnifying endoscopy of the same site noted irregularity of the blood vessels and tumor exposure see in (Figure 2).

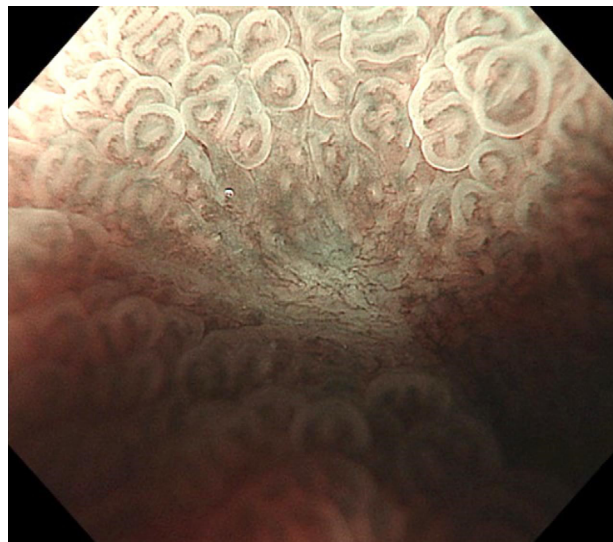


Figure 2: Magnified Narrow-Band Imaging (NBI) observations. The surface structure of the depressed surface has disappeared, and tumor blood vessels with different calibers are visible.

EUS revealed a hypoechoic mass with internal heterogeneity and a heterogeneous shape, mainly situated in the second and third layers of the stomach wall. The tumor boundary was relatively clear, and no infiltration into the fourth layer was observed see in (Figure 3).

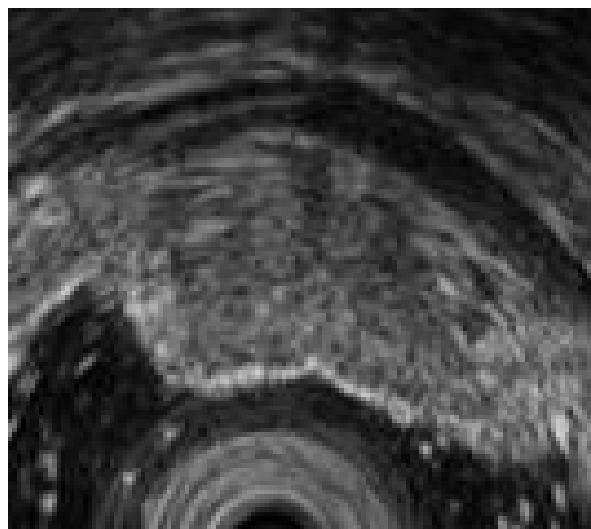


Figure 3: Endoscopic ultrasonography. The lesion is present in the second and third layers of the stomach wall. A hypoechoic mass with internal heterogeneity and a heterogeneous shape is observed.

The patient underwent EUS-guided fine-needle aspiration biopsy. The results of pathological examination showed a NET G1-equivalent. Contrast-enhanced computed tomography did not reveal any metastatic lesions. Blood tests showed that the patient was negative for parietal cell and intrinsic factor antibodies. Hormone levels were within normal limits, with an insulin level of 10.1 $\mu\text{U/mL}$, a glucagon level of 9.5 pg/mL , and a gastrin level of 72 pg/mL . Based on the above findings, the patient was diagnosed with a Rindi Type III gastric NET G1. According to the National Comprehensive Cancer Network guidelines [3], we proposed surgery. However, the patient was elderly and did not wish to undergo surgery because of which we decided to perform an endoscopic submucosal dissection (ESD). Pathological examination of the lesion resected by ESD, revealed a NET G2, T1b2 (2,000 μm) see in (Figure 4).

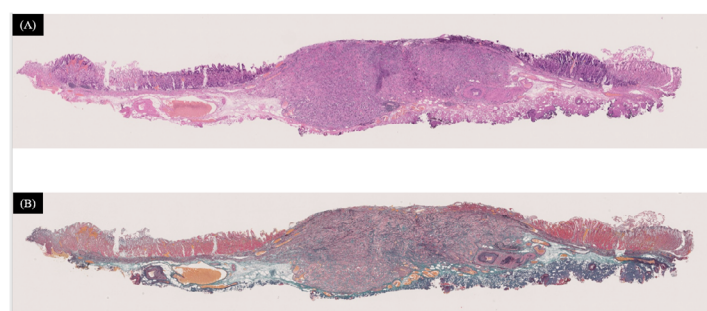


Figure 4: (A) Hematoxylin eosin (HE) image of a specimen removed by endoscopic submucosal dissection (loupe). (B) Elastica-Masson staining (loupe). Elastic fibers are stained dark brown, while collagen fibers are stained green. In the tumor, there is a mix of elastic fibers and collagen fibers.

The size of the tumor was 6×7 mm. A small portion of the tumor was exposed at the mucosa, although most of the tumor cells containing a small oval nucleus infiltrated into the submucosal layer. The biopsy results reported a G1-equivalent tumor, although the final diagnosis was of a G2 tumor. The horizontal and vertical margins were negative. There was no lymphovascular invasion. The Ki67 index was 8.4% within the hot spot. Immunostaining showed that the tumor was positive for chromogranin, synaptophysin, SSTR2A, and VMAT2. However, the tumor was negative for insulin, glucagon, gastrin, and somatostatin. Due to the prominent fibrous stroma within the tumor, we stained the tumor specimen for serotonin and found some of the cells to be positive for serotonin see in (Figure 5). The patient remains recurrence-free 36 months postoperatively.

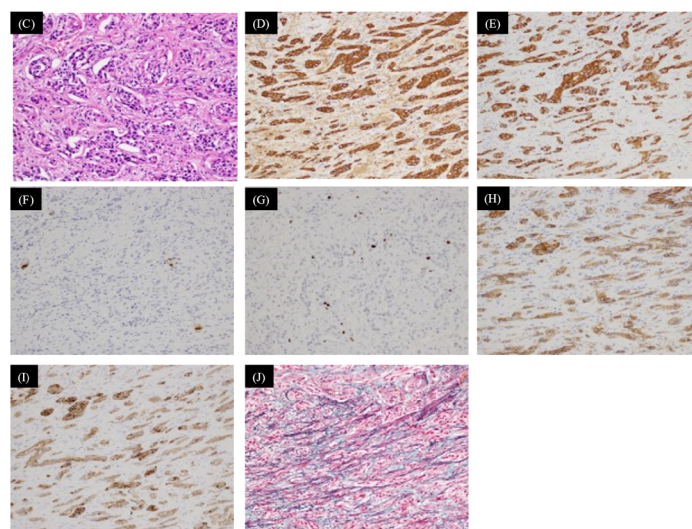


Figure 5: (C) HE staining ($\times 200$); (D) immunostaining for chromogranin A ($\times 200$), (E) synaptophysin ($\times 200$), (F) serotonin ($\times 200$), (G) Ki67 ($\times 200$), (H) SSTR2A ($\times 200$), (I) and VMAT2 ($\times 200$); and (J) Elastica Masson staining ($\times 200$).

Discussion

The World Health Organization classification of gastrointestinal neuroendocrine neoplasms (NENs) was revised in 2019 when it became clear that an NET and neuroendocrine carcinoma are different pathologies that arise due to genetic abnormalities and the effects of therapeutic drugs [4]. Approximately 44% of gastrointestinal NEN cases are discovered incidentally despite being asymptomatic on screening endoscopy [5]. Rindi et al. classified gastric NETs into three categories according to the presence or absence of hypergastrinemia and background diseases. This classification is used to this day. Type III disease is a solitary tumor, often ≥ 1 cm at diagnosis, and is considered to be highly malignant [6].

For gastrointestinal neuroendocrine tumors, the relationship between serotonin and fibrosis in each organ has previously been reported [7]. Serotonin-positive tumors are common among pancreatic NET cases, accounting for 1 to 4% of all cases [8,9]. However, there have been almost no cases exhibiting hyperserotonemia and the majority were of non-functional NETs.

This patient exhibited a curious pathological presentation. In general, hematoxylin and eosin staining of a gastric NET does

not show fibrous components. Because a gastric NET consists of a uniform lump of cells, EUS typically shows a uniform hypoechoic mass, similar to a lymph node. However, in this patient, pathological examination of the specimen, removed by ESD, showed a lesion with a fibrous stroma throughout the tumor.

As mentioned previously, this fibrous stroma was thought to be related to serotonin produced by the tumor. In this patient, the serotonin-positive cells accounted for around 10% of the entire tumor, and these cells tended to be scattered throughout the lesion. Although there are many reports of pancreatic NETs producing serotonin, to the best of our knowledge, there are no reports of gastric NET cases. The underlying mechanism reportedly involves activation of the ERK pathway by serotonin receptors, which leads to stimulation of DNA synthesis in fibroblasts, and fibroblast cell division [10].

The presence of a fibrous stromal component throughout the tumor may be the reason for the non-uniform hypoechoic overall appearance of the tumor in this patient. In other words, the hypoechoic mass with a non-uniform shape may not only reflect the tumor component but also the fibrosis, which may be different from the usual NET presentation.

Conclusion

Fibrosis due to serotonin production may lead to an atypical EUS presentation of gastric NETs, and one should proceed with EUS-based diagnosis of the tumor while keeping this in mind.

Consent

Written informed consent was obtained from the patient and is available upon request.

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