CASE REPORT

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Synchronous appearance of gastrointestinal stromal tumor and neuroendocrine tumor in stomach: Review of the literature and management strategies

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Gastrointestinal stromal tumors represent the most common mesenchymal tumor of the digestive tract. Although the stomach is the most common location for gastrointestinal stromal tumor with the co-primary tumors, the synchronous appearance of a neuroendocrine tumor and gastrointestinal stromal tumor in the stomach is rare. We present here the case of a 48-year-old male with gastric well-differentiated neuroendocrine tumor and gastrointestinal stromal tumor discovered incidentally during surgical treatment of the neuroendocrine tumor. We discuss the current guidelines for the management of small gastrointestinal stromal tumors (<2 cm in diameter) and the gastric carcinoids. We also review the literature for the co-occurrence of gastrointestinal stromal tumor and neuroendocrine tumor in a gastric location.

Key words: Gastrointestinal stromal tumor, neuroendocrine tumor, gastric carcinoid, carcinoid tumor, hypergastrinemia, endoscopic ultrasound

Midede gastrointestinal stromal tümör ve nöroendokrin tümör birlikteliği; literatür ve tedavi yaklaşımının gözden geçirilmesi

Gastrointestinal stromal tümörler sindirim sisteminin en sık görülen mezenşimal tümörüdür. Mide, gastrointestinal stromal tümörler ve ona eşlik eden primer tümörler için en sık lokalizasyon olmasına rağmen midede gastrointestinal stromal tümör ve nöroendokrin tümör birlikteliği son derece nadirdir. Bu makalede 48 yaşında erkek hastada iyi diferansiye nöroendokrin tümör ve bunun cerrahi rezeksiyonu sırasında tesadüfen bulunmuş bir gastrointestinal stromal tümör birlikteliğini sunuyoruz. İlaveten küçük boyutlu (<2 cm) gastrointestinal stromal tümörler ve nöroendokrin tümörlere yaklaşım konusunda güncel rehberleri tartışıp midede her iki tümörün birlikteliğine ilişkin literatürü gözden geçireceğiz.

Anahtar kelimeler: Gastrointestinal stromal tümör, nöroendokrin tümör, gastrik karsinoid, karsinoid tümör, hipergastrinemi, endoskopik ultrasonografi

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) represent the most common mesenchymal tumor of the digestive tract. Since 1998, after the recognition of the central role of KIT protein expression in these tumors, a number of papers have been published regarding the coexistence of other tumors with GIST (1-7). The major types of GIST-associated malignancies are the gastric epithelial tumors (5,6). Although the stomach is the most common location for both GISTs and the accompanying non-GIST tumors (7), the synchronous appearance of a neuroendocrine tumor (NET) and GIST in the stomach is rare.

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Gastric NETs, which have been variably termed carcinoid tumors, constitute about 1% of gastric neoplasms and 9% of GI tract carcinoids (8,9). We report here a case presenting with synchronous type-1 carcinoids and GIST in the stomach.

CASE REPORT

A 48-year-old male was admitted to our unit for gastric nodular lesions ranging in size from 0.5 to 1 cm, scattered at the fundus. Biopsies from the lesions and the surrounding normal tissue revealed well-differentiated NET and neuroendocrine hyperplasia, respectively.

He complained of dyspepsia. His fasting serum gastrin and chromogranin levels were elevated [966 (normal range: 13-115) pg/ml and 600 (range: 19-98) µg/L, respectively].

Subsequent abdominal computed tomography (CT) and somatostatin receptor scintigraphy were unremarkable. Endoscopic ultrasound (EUS) investigation reported hypoechoic lesions in the gastric submucosal layer. Because of the neuroendocrine hyperplasia in the surrounding mucosa and numerous nodules (more than 10) that demonstrated NET, surgery was planned instead of endoscopic resection. During the operation, an incidental exophytic mass measuring 1x1x1 cm in the greater curvature was observed, and total gastrectomy was thus performed.

Macroscopically, the gastrectomy specimen revealed submucosal nodules ranging from 0.2 to 1 cm and a subserosal grey-white mass of 1 cm in diameter originating from the muscularis propria. Histopathologically, submucosal nodules showed tumors composed of nests and tubuli of round cells with uniform nuclei and scant eosinophilic cytoplasm, which were immunoreactive with neuron-specific enolase, synaptophysin (Figure 1) and chromogranin-A . The subserosal mass revealed a tumor composed of spindle cells with uniform fusiform nuclei, which were immunoreactive for CD117 and CD34 (Figure 2). Less than 2% of tumor cells were stained with Ki67 antibody. Chronic atrophic gastritis was noted. *Helicobacter pylori* infection was not observed. Resection margins were free of tumors. No evidence of metastasis was found in any of the nine regional lymph nodes resected. Eventually, well-differentiated NET and a coexisting GIST in the stomach were diagnosed. Eight months after the surgery, there were no signs of relapse and the serum chromogranin-A level was within the normal limits.

DISCUSSION

Synchronous GIST and carcinoid in the stomach is rare, and to our knowledge, there have been only five case reports published in English (2,10-13). Two of them presented with incidental GIST, as in our case, while treating the carcinoid (10,11). One case had type-1 carcinoid (10); gastrin levels were not assessed in two cases (2,13), and the carcinoids in the other two cases were type-3 (11,12). Additionally, four cases of gastric GIST-NET co-occurrence were reported in a series, the details of which could not be retrieved (3). Clinical findings and tumor features of those cases are summarized in Table 1.

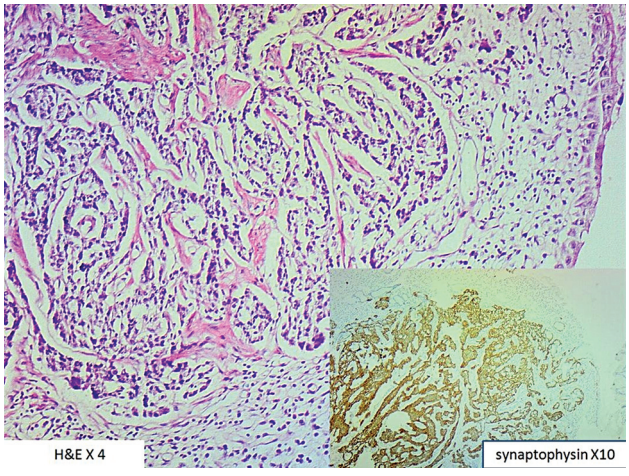

Figure 1. Neuroendocrine tumor (H&E, x4). Cells were immunoreactive with synaptophysin (x10).

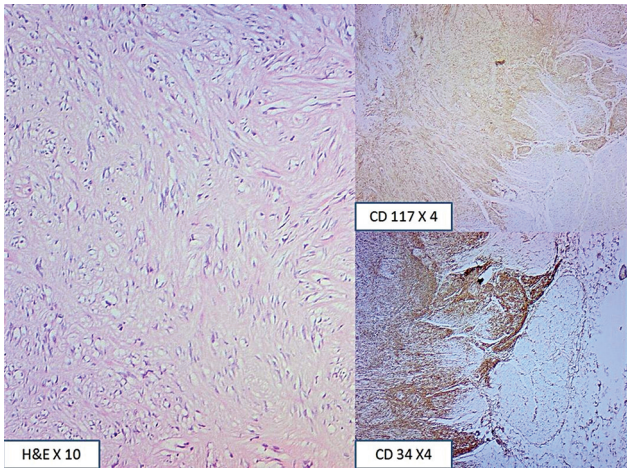

Figure 2. Gastrointestinal stromal tumor of spindle cell type (H&E, x10). Cells were immunoreactive with CD117(x4) and CD34(x4).

Table 1. Clinical and tumor findings of patients with synchronous GIST/Neuroendocrine tumor

Age/ gender	Symptom	Location NET/GIST	NET size (cm)	GIST size (cm)	Gastric NET	Treatment	Follow-up	*H. pylori*	Reference
65 F	None	Upper corpus	0.8	1.1x0.7	Type 3	Surgical resection	28 mon	+	11
65 F	Not given	Cardia	1.2	0.6	Type 1	Total gastrectomy	6 mon	-	10
58 M	Not given	Cardia/corpus	0.4	3.5	Type 3	Subtotal gastrectomy& reconstruction	1 year	-	12
69 M	Epigastric pain, nausea	Corpus	0.6	5x3	NA	Surgical resection	DUC at 12 m	-	2
79/M	Hemorrhage	Pylorus/ Corpus	1	0.5	NA	Total gastrectomy	NA	NA	13
48 M	Dyspepsia	Upper corpus	0.2 to 1	1x1	Type 1	Total gastrectomy	6 mon	-	Current paper

NA: not assessed, DUC: Died of unrelated causes, NED: no evidence of disease, F: female, M: male.

GISTs are mesenchymal tumors arising from a common precursor, the interstitial cells of Cajal. They may occur anywhere along the digestive tract, though the stomach is the most frequently involved site (40–60% of all cases). They are positive for CD117 (95% of cases), CD34 (60–70%), smooth muscle actin (30-40%), and desmin (2%) (13). GISTs may synchronously associate with other tumors, with an incidence of up to 27%, which may be considered as a high frequency (4). However, co-occurrence of GIST and NET in the stomach has not been reported in the large series, all of which were retrospective (5,7).

Our patient had type-1 gastric carcinoid tumor as was evidenced by the presence of hypergastrinemia. As in our case, tumors are usually small and multiple, limited to the mucosa-submucosa, and metastases to lymph nodes or liver occur in less than 2.5%. Patients with more than six polyps generally require more aggressive management than endoscopic resection (9). Antrectomy in patients with numerous type-1 gastric carcinoids arising in the setting of chronic atrophic gastritis may eliminate the source of gastrin production, resulting in tumor regression (9). Our patient had more than 10 carcinoid nodules with neuroendocrine hyperplasia in the surrounding mucosa. Therefore, the initial decision was to perform an antrectomy, but exploration of the GIST during the operation led us to perform a gastrectomy.

Simultaneous appearance of NET and GIST in the same organ raises the question of whether such an occurrence is a simple coincidence or whether both lesions are connected by a common causal relationship. *H. pylori* infection was once cited as a risk factor in the pathogenesis. However, four of the six cases reported in the literature were *H. pylori*-negative despite their advanced ages (Table 1). A relationship between gastric adenocarcinoma and gastric carcinoids has been hypothesized earlier through the elaboration of growth factors by the neuroendocrine cells and ultimate phenotype alterations in the adjacent mucosa (15). The role of chronic atrophic gastritis also deserves to be studied because it was reported in three of the six cases (Table 1). Obviously, further studies are needed to clarify the association of GIST with NET in the stomach.

The National Comprehensive Cancer Network (NCCN), European Society for Medical Oncology (ESMO) and Japanese GIST guidelines indicate that gastric GISTs ≥2 cm should be excised, whereas the Canadian Advisory Committee indicates that even small GISTs <1 cm should be excised because of the risk of metastasis. The NCCN guidelines state that the proper management of small GISTs (<2 cm) discovered incidentally remains controversial, while ESMO and Japanese guidelines recommend EUS and then follow-up due to the recognized difficulty of biopsy of those small tumors, reserving excision only for nodules that increase in size or develop symptoms such as bleeding. However, as in our case, GISTs maybe missed upon EUS investigation when the diameter of the GIST is small (<1 cm). In short, surgery remains the mainstay of treatment for gastric GISTs ≥2 cm, but management of incidental small GISTs (<2 cm) remains somewhat controversial despite the publication of comprehensive guidelines (14). Risk of an aggressive clinical course based on tu-

mor size, mitotic count and location should be stratified for each case after the resection. Obviously, resection of our patient's GIST of 1 cm that was discovered incidentally should not be taken as overtreatment according to the guidelines addressed above.

In conclusion, GIST and NET may appear synchronously in the stomach at an incidence probably higher than was appreciated before because of the incidental discovery of one tumor while evaluating the other. Therefore, special effort may be given to check for their existence before scheduling the therapy.

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