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Synchronous Gastric Adenocarcinoma and Incidental Gastrointestinal Stromal Tumor

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Background	Gastric adenocarcinomas (GA) are commonly encountered malignancies of the stomach. However, the synchronous presentation of GA with gastrointestinal stromal tumors (GISTs) is rare. A preoperative diagnosis of concurrent GIST can be difficult because GISTs often evade detection from routine upper endoscopies. This study describes a case presentation of synchronous GA with GIST and the findings of a literature review.
Summary	We report a case of a 79-year-old male who presented with biopsy-confirmed GA. His only symptom was new-onset recurring dysphagia and a relevant past medical history of gastritis. He denied symptoms of hematemesis, melena, hematochezia, weight loss, or abdominal discomfort. A laparoscopic partial gastrectomy with Roux-en-Y reconstruction was performed. During surgery, two gastric lesions were subsequently removed and biopsied. Histological analysis of the larger gastric lesion confirmed the presence of intestinal-type GA. Immunohistochemistry analysis of the smaller lesion was positive for KIT, DOG1, actin, and desmin, indicative of GIST. The final diagnosis was most consistent with synchronous GA and GIST.
Conclusion	Synchronous GA and GIST is an uncommon neoplasm. We discuss the findings of a literature review, disease characteristics, diagnostic modalities, and available treatment. Early detection and treatment of synchronous GA and GIST may be beneficial in improving patient survival.
Key Words	gastrectomy; endoscopic ultrasonography; gastrointestinal stromal tumor; adenocarcinoma; collision tumor

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Case Description

Gastric cancer is the third leading cause of cancer deaths worldwide; in the United States, gastric cancer has a five-year relative survival of 32%.[1-3] Incidence and mortality from gastric cancer are the highest in Asian countries, and 95% of gastric cancers are histologically adenocarcinomas.[2] Gastrointestinal stromal tumors (GISTs) represent less than 1% of all gastrointestinal tumors but are the most common type of mesenchymal tumors to arise from the alimentary tract.[4] The concurrent finding of gastric adenocarcinomas (GA) and GISTs are uncommonly identified and reported. We present a patient diagnosed with synchronous GA and GIST who was subsequently treated with laparoscopic partial gastrectomy and Roux-en-Y reconstruction. We also present a literature review of previously reported case reports.

A 79-year-old male with a past medical history of gastritis, hypertriglyceridemia, and diverticulosis reported a new onset of recurring dysphagia. The patient denied symptoms of hematemesis, melena, hematochezia, weight loss, abdominal discomfort, or chest pain. He denied alcohol or tobacco use. The patient's gastroenterologist performed an upper endoscopy with biopsy, which identified adenocarcinoma of the gastric incisura. The patient was promptly referred to the general surgery clinic. A preoperative computed tomography (CT) did not demonstrate lymphadenopathy. After thorough review and consultation, a laparoscopic partial gastrectomy with Roux-en-Y gastrojejunostomy was performed. Care was taken to ensure that at least 3–5 cm of the proximal and distal margins were free of tumor, and the remaining gastrojejunostomy as well as the jejunojejunostomy, appeared healthy.

Pathologic assessment of the resected gastric mucosa revealed a 2 × 2 cm indurated mass with raised edges. Histology analysis confirmed the presence of a well-differentiated, intestinal-type GA. Proximal to the lesion was a 0.5 × 0.3 cm calcified exophytic nodule. Immunohistochemical analysis was positive for actin, c-KIT (CD117), DOG1, and desmin, most consistent with a GIST. Mitotic activity ≤ 5 per 5 mm^2 was indicative of a low-grade GIST. Pathology was able to isolate eight lymph nodes that were uninvolved by either metastatic adenocarcinoma or GIST. The final diagnosis was most consistent with GA in situ with incidental GIST. Postoperatively, the patient was scheduled to follow up with oncology, gastroenterology, and surgery. The oncologist ordered a postoperative positron emission tomography scan (PET), and the patient was set to be re-scoped in six months.

Discussion

Synchronous GA and GIST have seldom been reported in the literature. A literature review was performed using PubMed with the search terms "gastric adenocarcinoma" or "gastric neoplasm" and "gastrointestinal stromal tumor" or "GIST." Studies were excluded if not published in English and if full texts were unavailable. From a total of 19 case reports, 20 patients were identified (Table 1).[5-23] Twelve patients (60%) were from Asian countries, 11 patients (55%) were males, and the average age of presentation was 71 years old. Commonly reported symptoms were often nonspecific such as abdominal pain, nausea, vomiting, and weight loss. Almost half of the patients (nine patients) had a preoperative diagnosis of GA and were later found on pathology reports also to have an incidental GIST. Only one patient was pre-operatively diagnosed with GIST via endoscopic biopsy. However, the seemingly incidental nature of GISTs cannot undermine the seriousness of the tumor due to the potential for perforation and metastasis. Of the 12 patients whose outcomes were recorded, four (33%) eventually succumbed to their disease. Furthermore, the presence of GISTs with specific symptoms may raise a red flag for the multiple syndromes associated with GISTs, such as neurofibromatosis type 1, Carney Triad syndrome, and Carney Stratakis syndrome.[24]

GISTs have been theorized to arise from the interstitial cells of Cajal. The most common cause of GISTs has been identified to be a gain-of-function mutation in c-KIT (CD117) in Exon 11, a type III transmembrane receptor tyrosine kinase. GISTs without a KIT mutation may be caused by a mutation in platelet-derived growth factor receptor alpha (PDGFRA), a single transmembrane glycoprotein involved in cellular proliferation. About 65-90% of GISTs have been associated with either a KIT or PDGFRA mutation.[25] Previous studies have found that GISTs with synchronous gastric carcinoma may be less associated with KIT mutations compared to GISTs occurring alone.[25,26] The synchronous presentation of GA and GIST has been largely thought to be coincidental. However, there has been growing interest in other possible explanations for their synchronous occurrence. Unknown carcinogens and/or inherent genetic mutations are being studied for their possible effect on the proliferation and oncogenesis of both gastric epithelial and stromal cells.[25]

While contrast-enhanced CT is the gold standard for assessing abdominal masses, lesions occurring in the stomach are an indication for upper endoscopy. Endoscopic ultrasonography (EUS) has been reported to be useful and reliable for tumors requiring further workup or having

Table 1. Summary of Literature Review. Published with Permission

Case	Author	Year	Country	Age	Sex	Presentation	Key Findings	Lymph node invasion	Intervention	Outcome
1	Bi et al	2009	China	73	F	Epigastric discomfort Melena Dizziness Fatigue	Preop biopsy: chronic non-atrophic gastritis Path: gastric adenocarcinoma and GIST	Yes	Proximal subtotal gastrectomy	N/A
2	Fan et al	2017	China	53	F	Asymptomatic	Path: a) gastric adenocarcinoma b) small cell carcinoma of esophagus c) local squamous carcinoma in situ d) GIST	No	Total gastrectomy Adjuvant chemo (oxaliplatin and paclitaxel)	Disease free at 12 months
3	Jeong et al	2011	South Korea	74	M	Asymptomatic	Preop biopsy: GIST Path: Gastric adenocarcinoma + GIST	No	Subtotal gastrectomy with local resection of hilar mass	N/A
4	Katsoulis et al	2007	UK	78	F	Dyspepsia Epigastric pain Weight loss	Preop biopsy: gastric adenocarcinoma Path: gastric adenocarcinoma and GIST	Yes	Total gastrectomy with splenectomy Roux-en-Y reconstruction	N/A
5	Khoshnevis et al	2013	Iran	64	F	Dyspepsia	Preop biopsy: gastric adenocarcinoma Path: gastric adenocarcinoma and GIST	No	Subtotal gastrctomy and Billroth-II gastrojejunal anastomosis Adjuvant therapy	Disease free at 4 months
6	Kleist et al	2010	Patient A: Norway Patient B: America	Patient A: 86 Patient B: 78	Patient A: F Patient B: M	Melena Nausea Faintness	Both: Path showed GIST and gastric adenocarcinoma Patient B path: additional malignant epithelial elements, bone metastases	Both: No	Patient A: gastric resection of tumor Patient B: wedge resection of tumor	Patient A: disease free at 11 months Patient B: deceased at 4 months post-op
7	Kountourakis et al	2008	Greece	72	F	Epigastric pain Anemia	Path: gastric adenocarcinoma and GIST	No	Subtotal gastrectomy Adjuvant therapy (cisplatin and fluorouracil)	Disease free at 7 months
8	Nakaya et al	2004	Japan	69	M	Generalized edema Fatigue Anemia	Large GIST tumor (21 x 15 x 9 cm) in lesser omentum Gastric adenocarcinoma	Metastasis present; no regional LN invasion	None due to patient decompensation	Patient deceased during hospital stay from acute renal failure
9	Namikawa et al	2016	Japan	58	M	Abdominal discomfort Right epigastric pain	Large GIST tumor (21 x 20 x 14 cm) in left upper peritoneal cavity compressing liver and pancreas Gastric adenocarcinoma	Yes	Neoadjuvant therapy (imatinib mesylate) Total gastrectomy, distal pancreatectomy and splenectomy Adjuvant therapy (fluoropyrimidine)	Disease free at 4 months
10	Narasimhamurthy et al	2010	India	65	M	Dyspepsia Weight loss	Preop biopsy: gastric adenocarcinoma Path: gastric adenocarcinoma and GIST	No	Subtotal gastrectomy	N/A
11	Ozgun et al	2009	Turkey	78	M	Abdominal discomfort Abdominal pain Vomiting	Spontaneous perforation of GIST (10 x 8 cm) Gastric adenocarcinoma	No	2 surgeries: 1) Tumor excision with adequate margins 2) Total gastrectomy and Roux-en-Y	N/A
12	Poulios et al	2013	Greece	81	M	Upper abdominal pain Dysphagia Anemia	Preop biopsy: gastric adenocarcinoma Path: gastric adenocarcinoma and GIST	No	Subtotal gastrectomy Lower esophagectomy	Disease free at 12 months
13	Rauf et al	2006	Pakistan	70	F	Epigastric pain Nausea, vomiting Weight loss	Preop biopsy: gastric adenocarcinoma Path: gastric adenocarcinoma and GIST	Yes	Total gastrectomy	Patient deceased (time of postop not reported)
14	Sailors et al	2005	USA	65	F	Weight loss Cramps Vomiting Constipation	Path: a) gastric adenocarcinoma b) GIST c) granular cell tumors	Not reported	Billroth II gastrojejunostomy	N/A
15	Sista et al	2013	Italy	70	M	Dyspepsia Chronic anemia Epigastric pain Melena Weight loss	Preop biopsy: gastric adenocarcinoma Path: gastric adenocarcinoma and GIST	Yes	Total gastrectomy Roux-en-Y reconstruction	N/A
16	Telugu et al	2016	India	63	M	Dysphagia Upper epigastric pain Belching	Preop biopsy: gastric adenocarcinoma Path: gastric adenocarcinoma and GIST	Yes	Neoadjuvant therapy Esophagogastrectomy Adjuvent therapy (EOX regimen- epirubicin, oxaliplatin, capecitabine)	Disease free at 7 months
17	Theodosopoulos et al	2011	Greece	80	M	Epigastric discomfort Nausea Weight loss Anemia	Preop biopsy: gastric adenocarcinoma Path: gastric adenocarcinoma and GIST	No	Subtotal gastrectomy Billroth-II gastrojejunal anastomosis Adjuvant therapy (imatinib)	Disease free 12 months
18	Toyoda et al	2009	Japan	83	F	Asymptomatic	Path: Adenocarcinoma and GIST	Yes	N/A (Patient denied) Path done on autopsy	Deceased due to progressive disease
19	Uchiyama et al	2007	Japan	74	M	Asymptomatic	Preop biopsy: gastric adenocarcinoma Path: gastric adenocarcinoma and GIST	No	Laparoscope-assisted distal gastrectomy Billroth I reconstruction	N/A

high-risk features of GIST, especially regarding preoperative histological diagnoses.[27] Immunohistochemistry may help support the diagnosis. A highly sensitive and specific marker is c-KIT (CD117), as almost 95% of GISTs have been reported to express it.[28] Other markers to consider are DOG1, CD34, SMA, desmin and S-100.[4]

Treatment of concurrent GA and GIST depends on the severity of disease. From our literature review, surgical treatment was the most common and consisted of either a total or subtotal gastrectomy. As most patients were diagnosed with gastric cancer before surgery, the operative plan was initially for treating GA.

For GA in situ, the treatment option consists of gastrectomy with lymphadenectomy. For more invasive disease, treatment ranges from subtotal to total gastrectomy and lymphadenectomy with or without chemotherapy.[29] While patients who undergo either subtotal or total gastrectomy have similar five-year survival rates, those who undergo subtotal gastrectomy have fewer complications, shorter hospital stays, and better nutritional status.[29] The preferred treatment of primary GISTs is wedge resection as opposed to classic gastrectomy.[24] While asymptomatic patients with benign GISTs < 2 cm may be treated conservatively with routine imaging, those who require surgery may undergo laparoscopic surgery if the GIST is five centimeters

or smaller.[30] This method may be acceptable given that a plastic bag is utilized to minimize the risk of seeding, and the tumors are not directly handled with forceps.[27] Furthermore, exploration of the liver and peritoneum may be useful as these are common locations for GIST metastases. If metastases are detected prior to surgery, neoadjuvant or adjuvant tyrosine kinase inhibitors may be indicated.[24]

GA in situ has a five-year survival rate of 90%.[31] Localized GIST has a five-year survival rate of 94%.[30] However, the synchronous occurrence of GIST with GA is associated with a lower overall survival rate compared to gastric GISTs alone. Patients with synchronous GIST and gastric cancer have a lower five-year overall survival rate of 57.8%.[32] Some indicators of prognosis and survival have been identified as patient age, risk stratification, postoperative oral imatinib, and synchronous gastric cancer.[32] The Memorial Sloan Kettering Cancer Center prediction tools, including a gastric cancer and GIST nomogram, may help calculate prognosis.

Conclusion

The synchronous occurrence of GA and GISTs is uncommonly reported. Due to the non-specific clinical presentation, this synchronous malignancy may be challenging to diagnose. As upper endoscopies have limitations in diagnosis, a EUS may be more useful.

Lessons Learned

The lower overall survival rate observed in patients with synchronous GA and GISTs suggests that early diagnosis and treatment are critical in disease prognosis and survival.

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