

Synchronous primary adenocarcinoma and gastrointestinal stromal tumor in the stomach: A report of two cases

Midede senkranöz primer adenokarsinom ve gastrointestinal stromal tümör: İki olgu sunumu

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Synchronous occurrence of epithelial and gastrointestinal stromal tumors (GISTs) in the stomach is uncommon. This association has often been detected incidentally on gastric mucosa or serosa, or occasionally intramurally, at surgery or gastroscopy for other reasons. Various hypotheses have been proposed regarding this simultaneous development, and it is not known whether or not such an association is a simple incidental coexistence or whether the two lesions are connected by a causal relationship. In this article, we report two cases of synchronous development of stromal tumor and adenocarcinoma incidentally detected in the stomach in two elderly patients.

Key words: Adenocarcinoma, gastrointestinal stromal tumor, synchronous development

Midede epitelial ve gastrointestinal stromal tümörlerin (GIST) senkranöz birlikteliği sık değildir. Bu birliktelik sıklıkla gastrik mukoza ya da seroza üzerinde, nadiren intramural olarak diğer nedenlerle operasyon veya gastroskopi sırasında rastlantısal saptanır. Bu simültane gelişim için çeşitli hipotezler ileri sürülmüştür ve böyle bir birlikteliğin basit rastlantısal bir birliktelik olup olmadığı veya iki lezyonun nedensel bir ilişkiyle bağlanıp bağlanmadığı bilinmemektedir. Bu makalede iki yaşlı hastanın midesinde rastlantısal olarak saptanan senkranöz gelişmiş iki stromal tümör ve adenokarsinom olgularını bildirdik.

Anahtar kelimeler: Adenokarsinom, gastrointestinal stromal tümör, senkranöz gelişim

INTRODUCTION

Synchronous occurrence of epithelial and gastrointestinal stromal tumors (GISTs) in the stomach is uncommon and only case reports have been reported in the literature (1-3). The largest published series (adenocarcinoma in 5 cases and carcinoma in 1) was reported by Maiorana et al. (1). This association has often been detected incidentally on gastric mucosa or serosa at surgery or gastroscopy for other reasons, and various hypotheses have been proposed regarding this simultaneous development. It is not known whether or not such an association is a simple incidental coexistence or whether the two lesions are connected by a causal relationship (1-3).

In this article, we report two cases of synchronous development of stromal tumor and adenocarcinoma

ma incidentally detected in the stomach, and discussed in light of the reported cases.

CASE REPORTS

Case 1

A 71-year-old man presented with nausea, vomiting, worsening abdominal pain over the previous two months, and weight loss of 9 kg in the previous 15 days. Laboratory findings were unremarkable. Esophagogastroduodenoscopy demonstrated a mass located on the antrum, proximal to the pylorus. Histological examination of the endoscopic biopsy revealed a poorly differentiated adenocarcinoma, and total gastrectomy was performed. During surgery, a well-circumscribed nodular

gray-white lesion, measuring 0.5 cm and located on the subserosa of the proximal corpus, was seen, which had no connection with the adenocarcinoma.

Macroscopic examination of the total gastrectomy identified an ulcerovegetative tumor 5.7x4.2x1.5 cm in diameter located on the lesser curvature of the antrum. Microscopically, the tumor was a poorly differentiated adenocarcinoma with focal extracellular mucin production. Serosa was infiltrated, and metastatic lymph nodules were present in both lesser and greater curvatures. In the non-neoplastic gastric mucosa, chronic gastritis with multifocal intestinal metaplasia was detected. *Helicobacter pylori* was not observed.

The microscopic examination of the subserosal solid nodular lesion showed that the stromal tumor was composed of spindle cells without any pleomorphism or atypia. Mitosis and necrosis were not observed. It was well demarcated from surrounding muscular tissue. In immunohistochemical examination, CD34 (1:25, M7168, Dako) (Figure 1)



Figure 1. Diffuse and strong CD34 immunostaining in stromal tumor of case 1 (AEC x 100)

c-kit (1:20, Ab-6, Neomarkers) (Figure 2) and vimentin (1:50, CloneV9, Neomarkers) (Figure 3) were diffuse and strongly positive; smooth muscle actin (SMA) (1:100, CloneA4, Neomarkers), S-100 protein (1:50, Clone4C4.9, Neomarkers) and desmin (ready to use, ZC18, Zymed) were negative in the lesion.

Case 2

A 77-year-old man was admitted with complaints of loss of weight, fatigue, and abdominal pain after

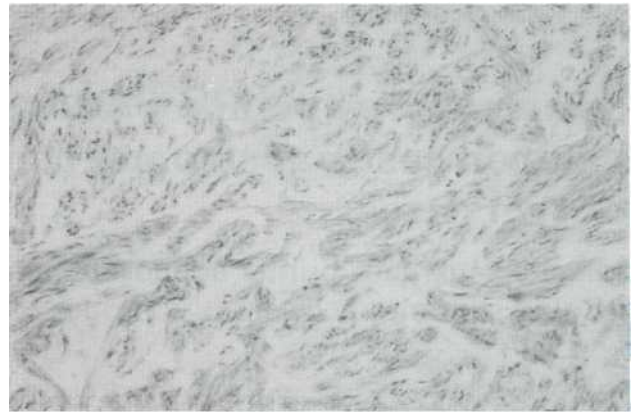


Figure 2. Positive c-kit staining in stromal tumor of case 1 (AEC x 100)

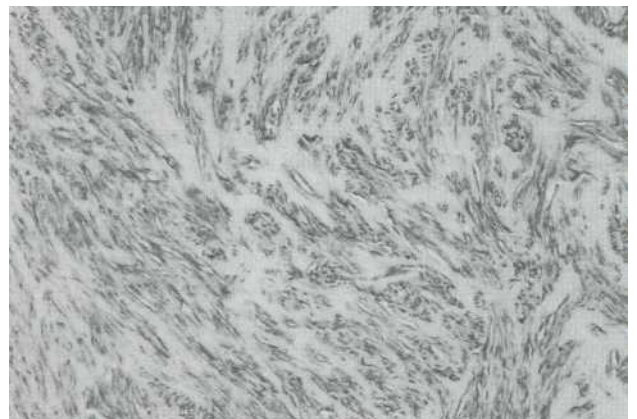


Figure 3. Positive vimentin staining in stromal tumor of case 1 (AEC x 100)

eating. His medical history revealed operations for nephrolithiasis and inguinal hernia, and he had undergone thyroidectomy and prostatectomy for benign disease. Laboratory findings were within normal limits. Esophagogastroduodenoscopy revealed an exophytic-vegetative mass located on the corpus of the stomach. Endoscopic biopsy showed a moderately differentiated adenocarcinoma, and the patient underwent total gastrectomy.

Macroscopic examination revealed a vegetative mass 7.5x6x2 cm in diameter located on the posterior wall of the corpus, and non-neoplastic gastric mucosa was smooth. Also identified in the submucosa of the gastroesophageal junction was a solid, gray-white, well-circumscribed nodular lesion, measuring 0.6 cm. Histological examination of the tumor showed moderately differentiated adenocarcinoma with tubulopapillary growth pattern.

Muscularis propria was infiltrated, but not serosa. Lymphovascular invasion and only one metastatic lymph node in the lesser curvature were detected. In the non-neoplastic gastric mucosa, particularly in the corpus, active chronic gastritis was detected, and the foci of intestinal metaplasia were observed. *Helicobacter pylori* was not detected.

Histological examination of the solid nodular lesion revealed an intramural stromal tumor consisting of spindle cells without any pleomorphism, atypia, mitosis or necrosis (Figure 4). It was well demarcated from surrounding muscle and connective tissue, and protruded to the submucosa. On immunohistochemical examination, the lesion stained diffusely and strongly with CD34, c-kit (Figure 5) and vimentin. SMA and desmin were focally positive, and S-100 protein was negative in the lesion.

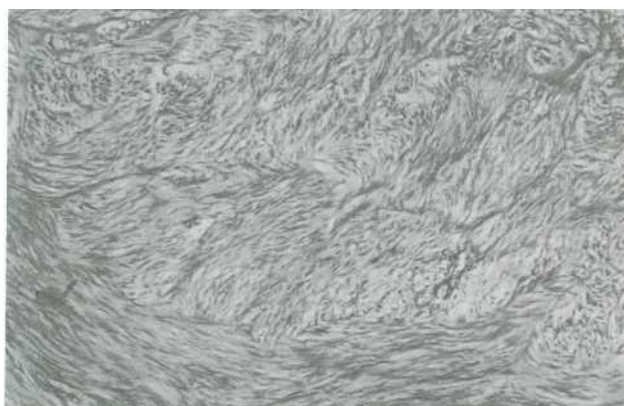


Figure 4. Stromal tumor consisting of spindle cells without any pleomorphism, atypia or necrosis in case 2 (HE x 100)

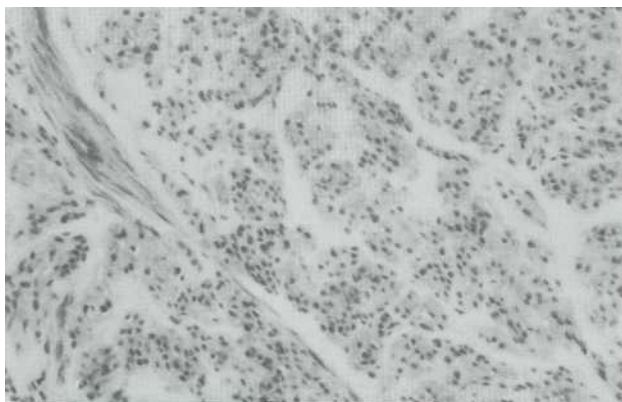


Figure 5. Positive c-kit immunostaining in case 2 (AEC x 200)

DISCUSSION

The simultaneous occurrence of gastrointestinal stromal tumor and adenocarcinoma in the stomach is uncommon in the literature. This association has been documented only as case reports (1-3). The largest published study in the literature consisted of six cases (adenocarcinoma in 5 cases and carcinoid in 1) (1). In addition to these synchronously occurring epithelial and stromal tumors, a case of collision tumor (4) and a case with two distinct mesenchymal tumors (GIST and lipoma) (5) have also been reported.

The majority of reported synchronous tumors were located in different regions of the stomach, such as antrum and corpus or lesser and greater curvatures (1-3). In two cases reported by Maiorana et al. (1), the neoplasms were closely juxtaposed, but did not merge, and they were separated by a thin normal gastric tissue. In our cases, adenocarcinomas were located in the corpus and antrum of the stomach, whereas GISTs were in the gastroesophageal junction and the serosa of the proximal corpus. In the published cases, the majority of epithelial tumors were usually intestinal type adenocarcinomas, except for one diffuse adenocarcinoma and two carcinoids. Inflammatory reaction was found in some cases, as chronic atrophic gastritis or active chronic gastritis. *Helicobacter pylori* infection and intestinal metaplasia or pancreatic acinar cell metaplasia were found in some cases (1-3). In our cases, moderately and poorly differentiated intestinal type adenocarcinomas were identified. In the first case, chronic gastritis with multifocal atrophy and in the second case chronic gastritis were detected. Widespread intestinal metaplasia accompanied these histological findings, but *Helicobacter pylori* was not present in the patients.

The definition of gastrointestinal stromal tumor excludes true smooth muscle tumors, such as leiomyoma, leiomyosarcoma and leiomyoblastoma, and schwannomas and neurofibromas. They are mostly seen in the stomach, followed in order of frequency by small intestine, colon and rectum, and esophagus. Microscopically, GISTs have spindle, epithelioid and occasionally pleomorphic cells (6-8). In the reported synchronous cases, the majority of stromal tumors were composed of spindle cells, except for one epithelioid tumor, and they were defined as benign, borderline and malignant. Although their location was often subserosa or submucosa, intramural development was also reported (1-3). In the cases of Maiorana et al.

(1), all stromal tumors stained positively and diffusely with vimentin, four tumors showed positive staining with CD34, whereas S-100 protein was focally positive, and muscle specific actin and desmin were negative. In the case of Kaffes et al. (3), the tumor stained positively with CD34, whereas staining with SMA, S-100 and desmin was negative. In both studies, however, the authors reported no information regarding c-kit staining. Andea et al. (2) reported multiple intramural stromal tumors, which were diffusely positive for CD34 and c-kit, focally positive for actin, and negative for S-100 protein. In our cases, vimentin, CD34 and c-kit were diffusely and strongly positive in both stromal tumors. SMA and desmin were focally positive, and the staining for S-100 was negative in the second case, whereas all those of the first stromal tumor were negative.

Small GISTs are often detected incidentally on gastric or small intestinal serosa during surgery for other reasons. They may also be detected during gastroscopy as submucosal nodules or as incidental radiologic findings (6-8). Histological diagnosis of the stromal tumor was not achieved preoperatively in any of the cases reported by Maiorana et al. (1). In these cases, GISTs were detected incidentally at surgery, and in four of six cases, adenocarcinoma was diagnosed preoperatively on biopsy fragments. The size of these stromal tumors was usually between 5 and 6 cm in diameter, except in one case in which it measured 0.6 cm, and they were located in the submucosa and subserosa of the stomach. Kaffes et al. (3) reported a case with three synchronous primary neoplasms of the stomach: adenocarcinoma, MALT lymphoma and GIST. In this patient, adenocarcinoma and lymphoma were diagnosed by preoperative endos-

copic biopsies, whereas a subserosal nodule, 1.5 cm in diameter, was found at laparotomy. In our presented cases, stromal tumors were found incidentally during surgery or at macroscopic examination, and the size of the two nodules was small when compared with the reported cases. In both patients, preoperative histological diagnosis was adenocarcinoma. The case reported by Andea et al. (2) was different from other reported cases due to the presence of multiple stromal tumors (measuring up to 1.2 cm) with coexistence of carcinoid and submucosal lipoma.

Maiorana et al. (1) proposed various hypotheses about synchronous occurrence of stromal tumor and adenocarcinoma, and considered whether or not such an association was incidental or whether the two lesions were connected by a causal relationship. Although they suggested that gene mutations or a single carcinogenic agent might interact with two neighboring tissues inducing the development of tumors of different histotypes in the same organ, they concluded that a coincidence alone could account for such an association, particularly in areas with high incidence rates of gastric cancer or surgery. Andea et al. (2) favored the former theory. According to the most recent theory, stromal tumors arise from the interstitial cells of Cajal (7-9), and at present, there is no evidence to link GISTs to *H. pylori* infection and/or to inflammation or intestinal metaplasia (3).

In summary, the simultaneous occurrence of gastrointestinal stromal tumor and adenocarcinoma is an uncommon finding. It seems to be related to incidence of gastric surgeries. Investigating the molecular alterations in such cases may reveal the etiology of this association.

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