

A Unique Simultaneous Presence of Adenocarcinoma, Carcinoid Tumor and gastrointestinal Stromal Tumor (GIST) in the Stomach

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Citation

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Abstract

Adenocarcinoma is the most common malignancy in stomach, whereas carcinoid tumor and gastrointestinal stromal tumor (GIST) only represent less than 1% , and approximately 1-3% of gastrointestinal tumors, respectively. Only a handful of cases of gastric collision/composite tumors with two distinct histological combinations (adenocarcinoma and carcinoid tumor, carcinoid tumor and GIST, adenocarcinoma and GIST) have been reported so far. Here we report a unique synchronous presence of an adenocarcinoma, carcinoid tumor and GIST in the stomach of a 75-year-old woman. To the best of our knowledge, this is the first case of such a triple entity occurring simultaneously in the stomach. The coexistence of multiple neoplasms from different tissue origin in the same organ is important from the viewpoints of epidemiology, histopathology, oncology, and surgery. It is our hope that this report could provide further awareness and insight into the entity of collision tumors.

INTRODUCTION

While adenocarcinoma is the most common gastric tumor originating from epithelial cells, carcinoid tumor which originates from the enterochromaffin-like (ECL) cells in the oxyntic mucosa, and gastrointestinal stromal tumor (GIST) which is believed to originate from the interstitial cells of Cajal, or its stem cell-like precursor, are relatively uncommon^[1,2]. Rare cases of simultaneous occurrence of epithelial tumors, neuroendocrine tumors, and stromal tumors in the stomach have been reported. There were thirteen cases of synchronous adenocarcinoma and GIST^[2,4,5,6,7,8,9,10,11], three cases of simultaneous carcinoid tumor and GIST^[8], and six cases of adenocarcinoma and concurrent carcinoid tumor^[3,12]. Our case represents an extremely rare event, and the only one in the literature which contains three types of primary neoplasms of histologically distinct origin in the middle third of the gastric body of a 75-year-old woman.

CASE REPORT

CLINICAL FINDINGS

A 75-year-old Hispanic female with a long standing history of pernicious anemia presented to our hospital with decreased appetite, early satiety, and 10-15 pounds weight loss over a 2 months period. She had no complaints of

abdominal pain, hemoptysis, melena, bright red blood per rectum, fever, yellowish discoloration of skin, or altered sensorium. However, she had multiple medical problems including: hypertension, hyperlipidemia; hypothyroidism; surgery and radiation for uterine cancer of unknown histological type diagnosed 7 years earlier, radiation-induced colitis; right lower extremity non-healing ulcer with biopsy showing granulation tissue, and eosinophilia of unknown duration. At the time of this presentation, an abdominal computed tomographic scan demonstrated a 5 x 2 x 1.5 cm fat-containing lesion in the right adrenal gland consistent with benign myelolipoma that was not removed, and Duplex Doppler study that showed bilateral femoral vein DVT. She was on multiple medications including Lotrel, Remeron, VitB12, Iron, Synthroid, Vytarin, Sulfasalazine, Elavil, and Lasix. She had no family history of cancer. A bulky polypoid ulcerated gastric mass was seen during an upper GI endoscopy. Biopsy revealed adenocarcinoma. Near-total gastrectomy (with a very small cuff of proximal stomach left behind) with Roux-en-Y gastrojejunostomy was successfully performed. Postoperative recovery was uneventful and was discharged. On follow up visit three weeks later she was found to be doing well.

GROSS FINDINGS

The gastrectomy specimen was fixed in 10% neutral

buffered formalin. It was opened along the greater curvature to reveal a 6.2 x 4.1 x 3.0 cm polypoid mushroom-shaped, pedunculated mass in the middle third of the gastric body with the attachment of the stalk base closest to the lesser curvature (Figure 1). The cut surface of the tumor was tan and white. Twenty-three lymph nodes in the lesser curvature and seven lymph nodes in the greater curvature were submitted for analysis.

MICROSCOPIC FINDINGS

Microscopic examination of the large polypoid mass revealed a moderately differentiated adenocarcinoma, invading the lamina propria of the stalk with clear margins (Figure 2). No vascular or perineural invasions was identified. In situ carcinoma was also present in the polyp. No evidence of malignancy was identified in thirty lymph nodes. In the stalk of the adenocarcinoma polyp, a different type of tissue proliferation was noted: it was composed of relatively smaller, monotonous tumor cells with granular cytoplasm and centrally located nuclei, mostly forming sheets of acini. It measured 0.6 cm in greatest dimension (Figure 3, A, B). Immunohistochemically, using a streptavidin-biotin horseradish peroxidase detection system (Dako, Carpinteria, CA), these tumor cells stained strongly and diffusely positive for both chromogranin (ICN Biomedicals, Aurora, OH) and synaptophysin (Dako, Carpinteria, CA) confirming the neuroendocrine origin of these tumor cells (Figure 4). The adenocarcinoma and carcinoid components in our case were entirely separated into adjacent but distinct areas, with no transition or intermixing between these two different tumors, indicating a collision pattern. The background gastric mucosa displayed features of chronic atrophic gastritis with marked intestinal metaplasia and absence of parietal cells (Figure 3, C). One 0.8 x 0.8 cm firm nodule with a tan cut surface was incidentally identified in the subserosa of gastric wall while searching for lymph nodes in the greater curvature. Histologically, this nodule was composed of spindle cells with high nuclear/cytoplasm ratio, and displaying a fascicular or storiform growth pattern. These tumor cells showed a diffuse and strong positive immunoreaction for CD117, and negative immunoreaction for smooth muscle actin (SMA) and desmin (all from Dako, Carpinteria, CA), consistent with GIST (Figure 5).

Figure 1

Figure 1: Stomach opened along the greater curvature revealing a large polypoid mass with its stalk attached on the lesser curvature.

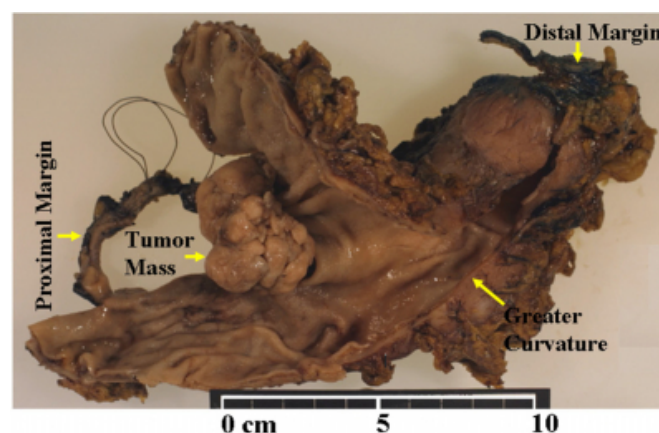


Figure 2

Figure 2: Moderately differentiated adenocarcinoma invading into the lamina propria of the stalk (hematoxylin-eosin, magnification x 2). (Inset, magnification x 40).

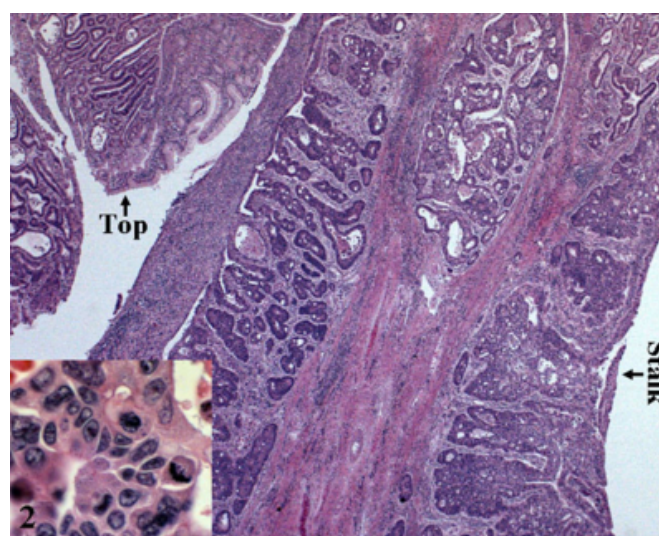


Figure 3

Figure 3: A, Carcinoid tumor in the stalk of the adenocarcinoma polyp (hematoxylin-eosin, magnification x 2). Solid arrow points to the carcinoid tumor, and the open arrow points to mucosa with chronic atrophic gastritis, and intestinal metaplasia. B, Higher magnification of carcinoid tumor (hematoxylin-eosin, magnification x 40). C, Chronic atrophic gastritis, and intestinal metaplasia (hematoxylin-eosin, magnification x 10)

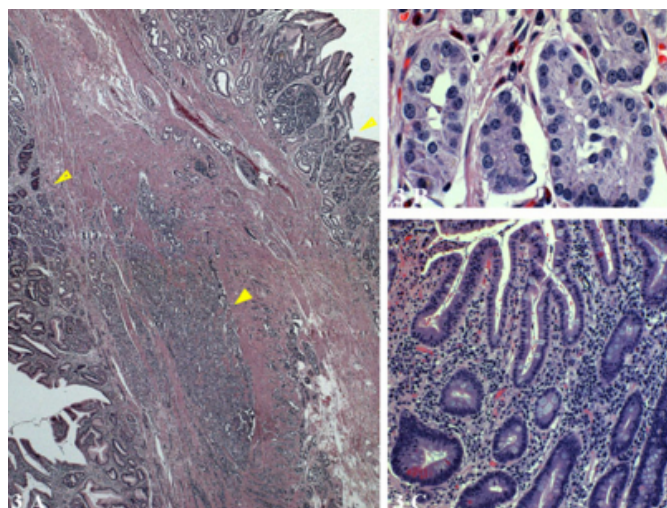


Figure 4

Figure 4: Immunohistochemical stains for neuroendocrine markers are strongly and diffusely positive on the carcinoid tumor (solid arrow) and hyperplastic neuroendocrine cells (open arrows). Magnification x 10. A, Chromogranin stain. B, Synaptophysin

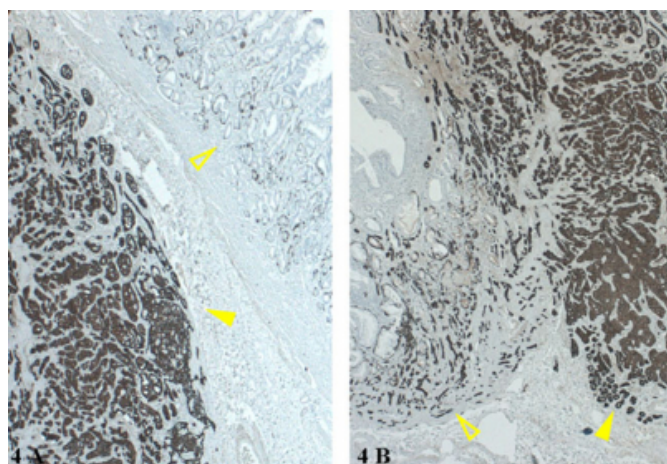
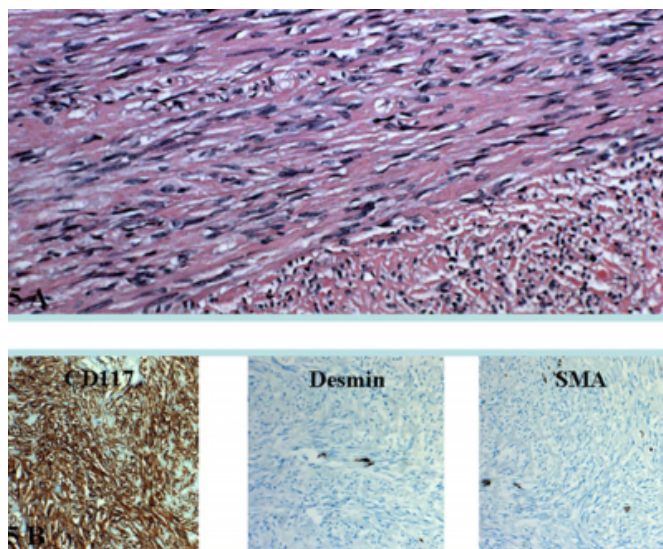


Figure 5

Figure 5: Gastrointestinal stromal tumor (GIST) in the subserosa of the gastric wall in the greater curvature (magnification x 20). A, Hematoxylin-eosin. B, Tumor cells are strongly and diffusely positive for CD117, but negative for Desmin and Smooth muscle actin.



DISCUSSION

Coexistence of a few primary dissimilar neoplasms in one patient is a rare phenomenon. Of special interest are cases in which one or more tumors were found within the same organ. Rare cases of simultaneous occurrence of epithelial tumors, neuroendocrine tumors, and stromal tumors in the stomach have been reported, which included thirteen cases of synchronous adenocarcinoma and GIST, three cases of carcinoid tumor and GIST, and six cases of adenocarcinoma and carcinoid tumor^[23456789101112]. Our case represents a very interesting and unique combination of all of the above three entities. There is a high incidence of microscopic GIST and carcinoid tumor foci in the stomach, and are therefore often discovered incidentally as in our case.

The development and progression of cancer is a multi-step process and the end result of interplay of many risk factors and protective factors^[1314151617]. In our case, the patient had a long history of pernicious anemia. Histologic examination revealed chronic atrophic gastritis and severe intestinal metaplasia (Figure 3, C). Although the exact risk is unclear, intestinal metaplasia and subsequent dysplasia are generally considered as premalignant lesions for adenocarcinoma^[1415].

Similarly, the link among parietal cell loss in atrophic gastritis, achlorhydria, and gastric carcinoid tumor is also well accepted. The achlorhydria leads to the loss of

inhibition of gastrin secretion, which in turn results in an increased gastrin production. The trophic effect of gastrin induces the proliferation of neuroendocrine cells (ECL cells), neuroendocrine hyperplasia, and eventually micro- and invasive-carcinoid^[16]. Indeed, we observed the whole spectrum of changes including chronic atrophic gastritis, neuroendocrine cell hyperplasia, and carcinoid tumor in our case (Figures 3 and 4). The chronic atrophic gastritis associated with pernicious anemia is thought to be an autoimmune disease and is historically classified as Type A chronic gastritis, in contrast to the Type B chronic gastritis associated with *Helicobacter pylori*. Carcinoid tumors associated with Type A chronic gastritis are classified as Type II^[1617].

On the other hand, gastrointestinal stromal tumor (GIST) is the most common mesenchymal tumor of the alimentary tract and consists of spindle, epithelioid, or pleomorphic cells^[18]. A mixed histological pattern is also common. GIST most likely derives from Cajal cells or related multipotential cells (pacemaker cells). A great majority of GIST occur in the stomach (60-70%) and small intestine (25-35%). There is no evidence to suggest the involvement of atrophic gastritis and intestinal metaplasia in the oncogenesis of GIST. Rather, the role of mutations involving CD117 and PDGFRA proto-oncogenes is well documented. GIST usually shows positive immunohistochemical reactivity with CD117 (c-kit) antibody. In addition, approximately 70% of GIST reacts positively to anti-CD34, 20-30% of GIST is SMA positive, 10% is S100 positive and it rarely shows positive reaction to anti-desmin. In rare instances, GIST occurs as part of tumor syndromes, like Carney's triad (gastric GIST, paraganglioma, and pulmonary chondroma), Neurofibromatosis type 1 (NF1) syndrome and familial GIST.

Recently, a multilineage progenitor cell (MPC) was identified in murine stomach epithelium which could regenerate the entire gastric gland including the neuroendocrine cells, and it was postulated that it is the MPC that actually accumulates the mutations which eventually lead to the carcinogenesis^[19]. Therefore, tumorigenesis of adenocarcinoma and carcinoid tumor could share the same pathway. At the molecular level, the most common genetic abnormality in adenocarcinoma is loss of heterozygosity of tumor suppressor genes especially p53 or "Adenomatous Polyposis Coli" gene^[15]. For carcinoid tumor, loss of MEN1 tumor suppressor gene encoded

MENIN and overexpression of growth factor Reg and the anti-apoptosis protein BCL-2 are involved^[16]. At this point, it is still not clear how these different molecular events interact with each other.

It has not been established whether the coexistence of a GIST with other unrelated syndromes or tumors is incidental or results from related pathophysiological processes. Our patient probably has a genetic predisposition to malignancy. Together with other contributing factors including radiation exposure, diet and other environmental factors, bacteria, hormones (gastrins, and somatostatins), it is reasonable to postulate that all these factors could potentially affect a number of molecular pathways such as apoptosis, proliferation, and differentiation, and eventually promote simultaneous aberrant overgrowth of different cell lineages, and eventually tumor formation^[1516171819]. Further integrated, multidisciplinary, multicentric investigation is apparently warranted to answer this question.

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