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Combined carcinoid and mixed (composite) glandular – endocrine cell carcinoma of the stomach in atrophic gastritis

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Summary

We describe a case of gastric carcinoid and inflammatory fibroid polyp concomitant with a composite tumor of the gastric antrum composed of poorly differentiated adenocarcinoma – endocrine carcinoma with immunohistochemical documentation of endocrine and non endocrine differentiation in a 67-year-old man with atrophic gastritis and intestinal metaplasia. When gastrectomy was carried out, two lymph nodes along the greater curvature harbored metastasis from carcinoid. The same occurrence is reported in several cases in the literature, which suggests that the association of gastric carcinoid to adenocarcinoma could point to the malignant nature of carcinoid. Furthermore, the findings in this patient reinforce the concept that the epithelial and neuroendocrine cells of the gastrointestinal tract both result from multidirectional differentiation of a primitive cell.

Key words: carcinoid, composite glandular-endocrine cell carcinoma, lymph node metastasis, stomach

Introduction

The development of adenocarcinoma or endocrine tumors in atrophic gastritis is widely documented [1-3]. Composite gastric tumors with an approximately equal proportion of glandular and endocrine cells are rare and only few well documented cases have been reported [4-8]. Our case is unique including 3 separate and histologically dissimilar gastric tumors: an inflammatory fibroid polyp, a well-differentiated tumor (carcinoid) and a composite tumor composed of poorly differentiated adenocarcinoma - endocrine carcinoma in a background of atrophic gastritis. In addition, two lymph nodes along the greater curvature had metastasis from carcinoid.

Case presentation

A 67-year-old man came to our hospital with epigastric pain and iron deficiency anemia. Except anemia, the results of serum biochemistry and urine were within reference ranges. CEA was within normal limit (3.6 ng/mL, reference range 0-5.0 ng/mL). His past medical history included essential hypertension, hyperlipidemia and cholecystectomy. There was no history of paraneoplastic endocrine symptomatology or family history of gastrointestinal diseases. Although physical examination did not provide additional information, further endoscopic examination revealed two polypoid lesions located in the anterior wall of the gastric body measuring 0.6 and 1.2 cm in diameter and a polypoid mass 5.5×5×4 cm in the antrum. Biopsy revealed features of both adenocarcinoma and endocrine tumor. A colonoscopy revealed edema and erythema of the mucosa, mainly at the transverse colon.

The patient underwent total gastrectomy. Intraoperative examination did not reveal alterations in other abdominal organs. On microscopic examination the first polypoid lesion (0.6 cm) corresponded to an inflammatory fibroid polyp and the second polypoid lesion (1.2 cm) was a typical carcinoid (well differenti-

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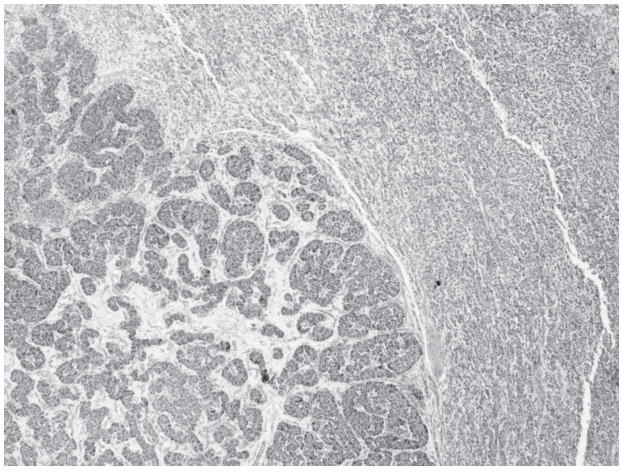

Figure 1. Carcinoid (H&E ×100).

ated endocrine tumor) with intramucosal and submucosal growth. It was composed of monomorph cells with granular cytoplasm arranged in a trabecular solid or sheet-like pattern (Figure 1). The cytoplasmic granules showed argyrophilia on Grimelius staining.

Immunohistochemically the tumor cells were positive for chromogranin A, synaptophysin and CD56 (Figures 2A, 2B). The expression of the cell proliferation marker Ki67 was low (<2%). Histologically the large polypoid mass was a composite tumor composed of poorly differentiated adenocarcinoma with mucinous deposits and poorly differentiated endocrine carcinoma with an approximately equal proportion of glandular and endocrine cells (Figures 3A, 3B).

The two components intermingled with each other in a similar proportion or were adjacently together. Both components of the tumor tissue invaded the mucosa and submucosa without extension to the muscularis propria.

The result of the immunohistochemical study demonstrated very strong immunoreactivity for chromogranin, synaptophysin and CD56 within the poorly differentiated endocrine carcinoma but no evidence of gastrin, insulin, somatostatin or pancreatic polypeptide (Figure 4). The expression of the cell proliferation marker Ki67 was high (>15%).

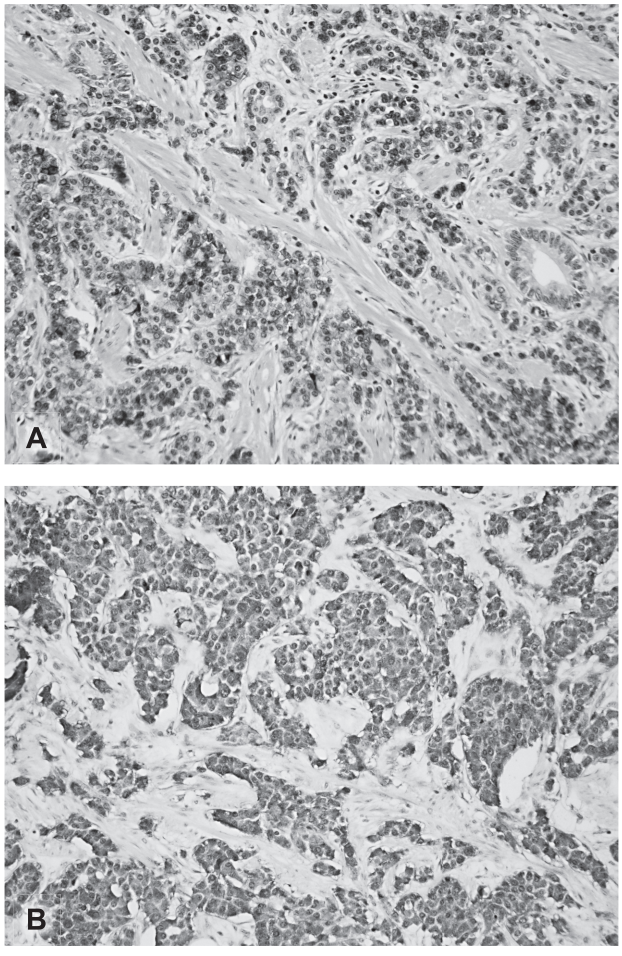

Figure 2. A: Carcinoid (CD56 ×200); **B:** Carcinoid (chromogranin ×200).

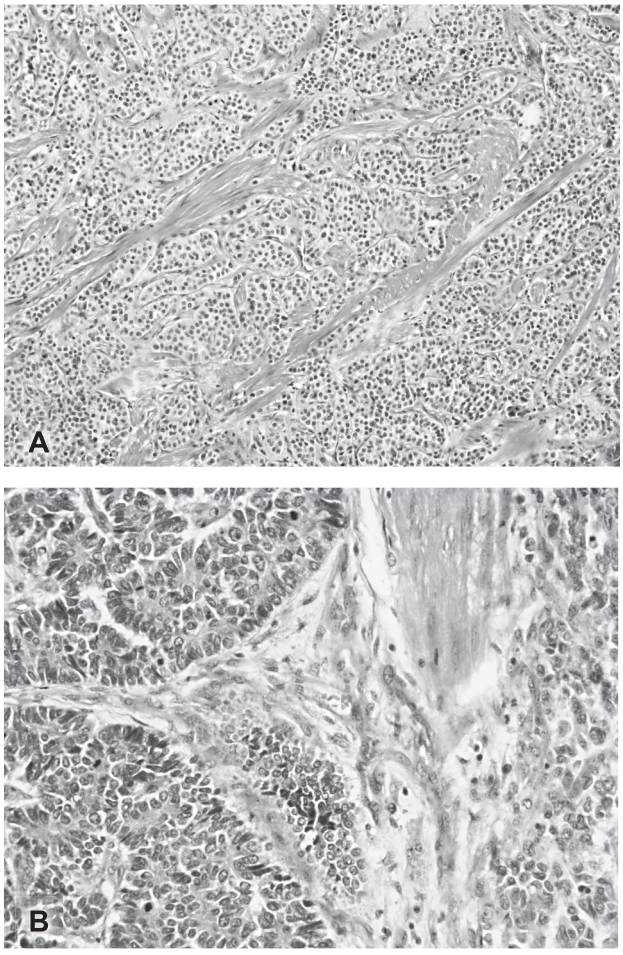

Figure 3. A: Composite adenocarcinoma-endocrine carcinoma (H&E ×40); **B:** Composite adenocarcinoma-endocrine carcinoma (H&E ×200).

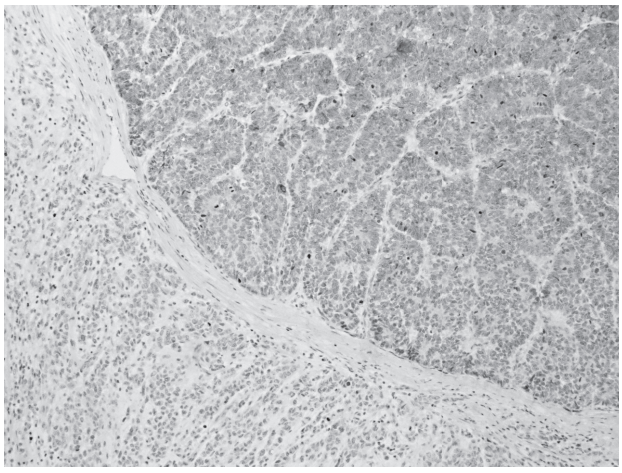

Figure 4. Composite adenocarcinoma-endocrine carcinoma (synaptophysin ×100).

A total of 15 lymph nodes were removed within the specimen. Each of them was cancer-free except two nodes along the greater curvature that harbored carcinoid metastasis. The gastric mucosa was characterized by atrophic gastritis with intestinal metaplasia. There was not *H. pylori* infection neither hypergastrinemia, usually associated gastric carcinoids or atrophic gastritis.

The postoperative outcome was uneventful. The patient was disease-free 6 months after the operation.

Discussion

Carcinoid tumors are the most common neuroendocrine tumors in the gastrointestinal tract and about 10-30% of them are gastric in origin. The prevalence of a gastrointestinal carcinoid tumor based on the original site differs in Japan and in the Western countries. Four types of gastric carcinoid have been identified: 1) multiple small body-fundus carcinoids associated with chronic atrophic gastritis type A; 2) sporadic solitary lesions without specific pathogenetic background; 3) carcinoid associated with multiple endocrine neoplasia; and 4) rare tumors such as neuroendocrine carcinomas and mixed endocrine-exocrine tumors [9-12].

The carcinoma-carcinoid spectrum is a concept of classifying tumors based on the tumor mass differentiated which is composed of tissues of both endocrine and nonendocrine functions. Multidirection differentiation in neoplasms is a phenomenon that has aroused particular interest in the case of the carcinoma-carcinoid spectrum [1,13,14]. Among the tumors of the carcinoma-carcinoid spectrum the most prevalent are carcinomas with interspersed endocrine cells [13]. The composite tumor is less common than carcinomas with interspersed endocrine cells. When two types of tissues exist intermingled with each other in a similar proportion, they are called "composite tumor" [6,7,13,15]. On the other hand, collision tumor is characterized by the presence of two localized tissue types adjacently together. Usually it is not easy to morphologically distinguish a collision type from a composite type tumor. It has been reported that metastasis from a composite tumor shows both of the tissue constituents, whereas those from a collision tumor shows only a single tissue component. There are 33 cases of gastric collision tumors composed of epithelial and non epithelial malignant neoplasm reported in the literature. Adenocarcinoma and malignant lymphoma was the most frequent finding. There were only 6 cases of adenocarcinoma and carcinoid tumor [15-17]. The occurrence of adenocarcinomas coexisting with carcinoids in the stomach is much less frequent ranging from 7.8 to 14% of all carcinoids. Also the development of adenocarcinoma or carcinoid tumors in atrophic gastritis is widely documented. Gastric composite tumors are relatively rare. The glandular-endocrine carcinoma of the stomach bears the following clinicopathologic features: it affects adults aged 30-74 years and has a male: female ratio of 1.3:1. It is located with almost equal frequency in the gastric body and antrum and has poor prognosis, similar to that of advanced classic gastric carcinoma [6]. Our case is an exceedingly rare case of a composite tumor of the gastric antrum composed of poorly differentiated adenocarcinoma and poorly differentiated endocrine carcinoma in a background of atrophic gastritis with histochemical and immunohistochemical documentation of endocrine and nonendocrine differentiation. Furthermore, there was a gastric carcinoid with no evident malignant features concomitant with the composite tumor. The major point of our report is the finding of nodal metastasis from the carcinoid which had no evident malignant features. The review of the literature suggests that the association of carcinoid to the adenocarcinoma points to a malignant nature of the carcinoid apart from the underlying gastric disease and tumor characteristics and regional or distant metastasis must be expected from the carcinoid component [18]. No clear clue exists to explain the malignant behavior of gastric carcinoids concomitant with adenocarcinomas. Some believe that the bioactive agents secreted by carcinoids might function as growth factors which may promote phenotypic changes in cells and induce neoplastic transformation [19,20].

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