

Composite Carcinoma of the Stomach Associated with Sarcoid-Like Granulomas

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Abstract Composite glandular/exocrine-endocrine carcinoma of the gastrointestinal tract is a special tumor type composed of common adenocarcinoma and the neuroendocrine component comprising at least one-third of the whole tumor area. These tumors are rare in the stomach and mostly published as case reports. We describe a further case of a 36-year-old man being unique in that it was associated with extensive formation of sarcoid-like granulomas. Tumor consisted of, predominantly poorly differentiated, intestinal-type adenocarcinoma and poorly differentiated neuroendocrine, small cell carcinoma. The adenocarcinomatous and neuroendocrine areas were separated, but closely juxtaposed with focal areas showing gradual transition from one to another. Perigastric lymph node metastases corresponded either to neuroendocrine or adenocarcinomatous component. On immunohistochemistry, the exocrine part was positive for cytokeratin 7, whereas superficial well-differentiated parts showed positivity with cytokeratin 20 as well. The neuroendocrine component was negative with those two types of cytokeratin. Both adenocarcinomatous and neuroendocrine tumor portions

showed carcinoembryonic antigen (CEA) immunopositivity. Neuroendocrine markers (chromogranin A, synaptophysin and neuron-specific enolase) were diffusely positive in the neuroendocrine component, and found only in the scattered cells within the neoplastic glands of the adenocarcinoma. Entire gastric mucosa and all perigastric lymph nodes were extensively affected by noncaseating, sarcoid-like granulomas. The absence of any clinical manifestations combined with the negative results of chest radiograph and laboratory test for the serum angiotensin converting enzyme argued against the possibility of systemic sarcoidosis.

Keywords Composite exocrine-endocrine carcinoma · Gastric carcinoma · Immunohistochemistry · Sarcoid-like granuloma · Stomach

Introduction

Human cancers displaying a combination of conventional (glandular, squamous or urothelial) and neuroendocrine (NE) features are a well-known occurrence in various organs [1, 2]. In the stomach, endocrine cells occur rather frequently within epithelial tumors in a spectrum ranging from classical adenocarcinoma at one end, through various types of mixed exocrine-endocrine tumors, to pure classical endocrine tumors (well- and poorly-differentiated) on the other end [1–10]. Broadly, epithelial tumors of mixed cell types, i.e. mixed exocrine-endocrine tumors of the stomach could be subdivided into six categories: 1) carcinomas with interspersed NE cells (adenocarcinomas with focal neuroendocrine differentiation); 2) carcinoids with dispersed neuroendocrine cells (goblet-cell carcinoids); 3) composite glandular/exocrine-endocrine cell carcinomas with areas of carcinoma (regardless of the degree of differentiation) and

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of carcinoid (also regardless of the degree of differentiation); 4) collision tumors in which endocrine tumors and adenocarcinomas are closely juxtaposed but not admixed; 5) amphicrine tumors composed predominantly of cells that exhibit dual endocrine and non-endocrine differentiation; and 6) tumors with combinations of the types cited above [6]. Tumors are classified as truly mixed—composite only if both exocrine and endocrine components are intimately intermingled within the same tumor mass and present in a significant proportions; i.e. endocrine cells must comprise at least one third to one half of an adenocarcinoma [4]. Mixed exocrine-endocrine carcinomas (MEEC) of the stomach are infrequent and in the WHO classification of gastric carcinoma they are only mentioned in the paragraph on the rare tumors of the stomach [11].

The occurrence of epithelioid cell granulomas, identical to those of systemic sarcoidosis, in primary tumors and lymph nodes draining malignant neoplasms is a well known phenomenon, mostly documented with gastric and breast carcinoma [12]. These histologic lesions have been termed “sarcoid reaction” [13]. The present report describes previously unpublished association of a composite exocrine-endocrine carcinoma of the stomach and extensive sarcoid reaction within gastric mucosa and perigastric lymph nodes.

Case Report

Clinical History

A 36-year-old man had undergone an upper gastrointestinal endoscopy for epigastric pain. A diagnosis of gastric tubular adenocarcinoma was made and the patient was referred to our hospital for surgery. His past medical and family histories were unremarkable. Physical examination on admission, routine blood tests and urine analysis were normal. A partial gastrectomy with omentectomy and regional lymph node dissection was performed. Postoperative recovery was uneventful, and the patient has been asymptomatic without evidence of recurrence or metastasis for the following 5 months. After the histopathological diagnosis had been established, the patient was investigated for the serum angiotensin-converting enzyme (s-ACE), with the additional chest radiography, and the inspection for skin and ocular lesions. ACE was 36.8 U/l (normal range: 8.0–52.0 U/l). A chest X-ray film, and skin and ocular examinations revealed no abnormal findings.

Pathologic Findings

Tissue samples were fixed in 10% formalin and routinely processed for microscopic analysis. Five μm thick sections

were stained with hematoxylin and eosin. Mitotic rate was expressed as the number of mitotic figures per ten high power fields (HPFs) in the mitotically most active area, using an $\times 40$ objective and an $\times 10$ ocular lens. Immunohistochemical stains were performed using the streptavidin-biotin technique with DAKO's LSAB+ kit (Dako, Glostrup, Denmark) with the following antibodies: pancytokeratin (Clone AE1/AE3; dilution 1:100; DAKO), cytokeratin (CK) 7 (OV-TL12/13; 1:50; DAKO), CK 20 (Ks20.8; 1:25; DAKO), carcinoembryonic antigen (CEA) (II-7; 1:25; DAKO), chromogranin A (DAK-A3; 1:200; DAKO), synaptophysin (polyclonal; prediluted; DAKO), neuron-specific enolase (NSE) (BBS/NC/VI-H14; prediluted; DAKO), Ki-67 (MIB-1; 1:25; DAKO), gastrin (polyclonal; 1:300; DAKO), somatostatin (polyclonal; 1:300; DAKO), serotonin (5HT-H209; 1:50; DAKO), glucagon (polyclonal; 1:25; Novocastra, Newcastle, UK) and insulin (2D11-H5; 1:100; Novocastra). For the heat-induced antigen retrieval, tissue sections were immersed in 0.01 mol/L citrate buffer (pH 6.0) and treated in a microwave oven for 20 min at 620 W for all the antibodies, except for insulin which was treated in pressure cooker for 2 min. The reaction products were visualized with diaminobenzidine, and the sections were counterstained with Mayer's hematoxylin. The percentage of positive tumor cells was recorded as follows: (+) <10% cells stained; (++) 10–50% cells stained; (+++) >50% cells stained. Proliferative activity assessed by the Ki-67 labelling index (LI) was expressed as the percentage of positive cells, calculated from the number of positive tumor cells per total number of tumor cells counted in the areas with the most pronounced immunopositivity. Counting was performed on images taken from two microscopic high-power fields with the Olympus DP70 digital camera (Olympus Corporation, Tokyo, Japan) using the Cell B software (Olympus Soft Imaging Solutions GMBH, Leinfelden-Echterdingen, Germany), with the screen grid and the manual touch-count method. For double immunostaining, anti-synaptophysin or anti-chromogranin A antibody was applied first, with DAB as a chromogen, followed by an additional 10-min microwave treatment and anti-CK7 as the second antibody, with AEC as a chromogen.

The gastrectomy specimen measured 22 cm along the greater curvature and 15 cm along the lesser curvature. An excavated antral tumor, 3.5 cm in diameter, on the greater curvature (Fig. 1a) appeared to invade into perigastric fat tissue. Perigastric lymph nodes were enlarged, firm and grossly abutting the wall of the greater curvature. Histological examination revealed the advanced gastric carcinoma with the involvement of the serosal surface. The tumor consisted of two distinct growth patterns: predominantly poorly differentiated tubular/intestinal type adenocarcinoma and the NE carcinoma. Adenocarcinomatous and NE component were separated, but closely juxtaposed with only rare areas of gradual

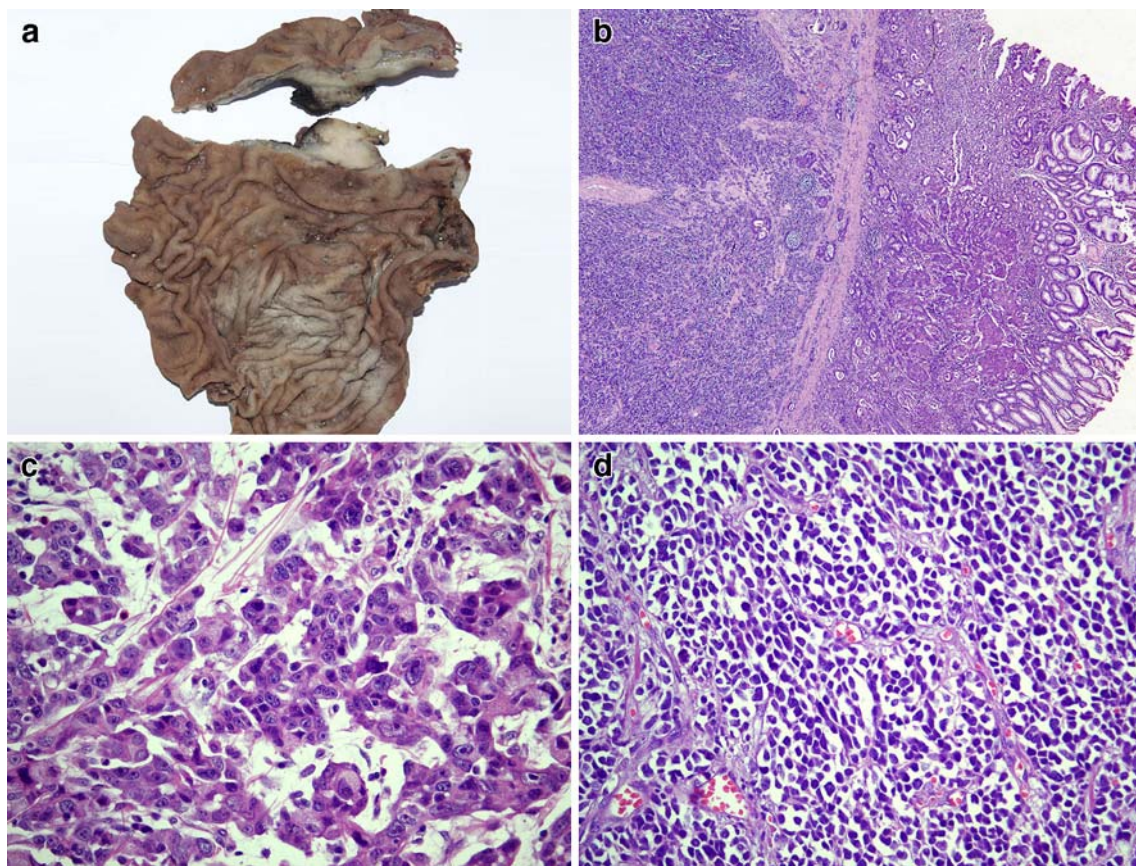


Fig. 1 Gross appearance of the composite carcinoma of the stomach after sampling for histological examination (**a**). The tumor consists of adenocarcinomatous (*right*) and neuroendocrine component (*left*) (**b**). Poorly differentiated adenocarcinoma exhibiting pleomorphic

cells with eosinophilic cytoplasm and atypical nuclei with large nucleoli (**c**). Neuroendocrine portion of the tumor with small round cells (**d**). (hematoxylin-eosin, original magnification: B, $\times 12.5$; C, D, $\times 400$)

transition from one to another (Fig. 1b). Multiple islands of NE carcinoma comprised together approximately one third of the whole tumor mass. The exocrine component consisted of small areas of well-differentiated adenocarcinoma in the upper parts of the tumor and predominant poorly differentiated adenocarcinoma in the deep portions of the tumor. The latter areas were composed of solid nests of large, pleomorphic cells with eosinophilic cytoplasm and atypical nuclei containing coarse chromatin and large nucleoli (Fig. 1c). Mitotic activity in adenocarcinomatous component was 6 mitoses/10 HPFs. The NE portions consisted of small, round or fusiform cells with scant cytoplasm and hyperchromatic nuclei (Fig. 1d), exhibiting 18 mitoses/10 HPFs, and arranged in trabecular and solid growth pattern. Seven of 34 perigastric lymph nodes analyzed contained metastatic deposits displaying adenocarcinomatous in five and NE component in two nodes. The entire gastric mucosa and all perigastric lymph nodes showed extensive involvement with noncaseating sarcoid-like epithelioid cell granulomas (Fig. 2a and b). Numerous giant cells within granulomas exhibited laminated Schau-

mann bodies, and some of them contained asteroid bodies (Fig. 2a, inset). An intimate relationship of granulomas and adenocarcinomatous tissue was identified at the mucosal level (Fig. 2c) as well as within lymph nodes.

Immunohistochemical results are summarized in Table 1. Pancytokeratin immunoreactivity was found in both adenocarcinomatous (well-, and poorly-differentiated) and NE component. Well-differentiated glandular areas were uniformly positive for CK7, CK20 and CEA. Scattered tumor cells in neoplastic glands of well-differentiated portions were positive for chromogranin A (Fig. 3a), synaptophysin and neuron-specific enolase. Tumor cells of the poorly differentiated adenocarcinomatous areas were also immunoreactive for CK7 and CEA, but negative for CK20 and all NE markers. NE component showed positivity for chromogranin A, synaptophysin (Fig. 3b), NSE and CEA. The immunoreactivity for gastrin, somatostatin, serotonin, glucagon and insulin was not detected. Ki-67 LI was 47% in well-differentiated (Fig. 3c) and 50.5% in the poorly differentiated adenocarcinomatous component (Fig. 3d), and 60.5% in the NE parts of the tumor (Fig. 3e).

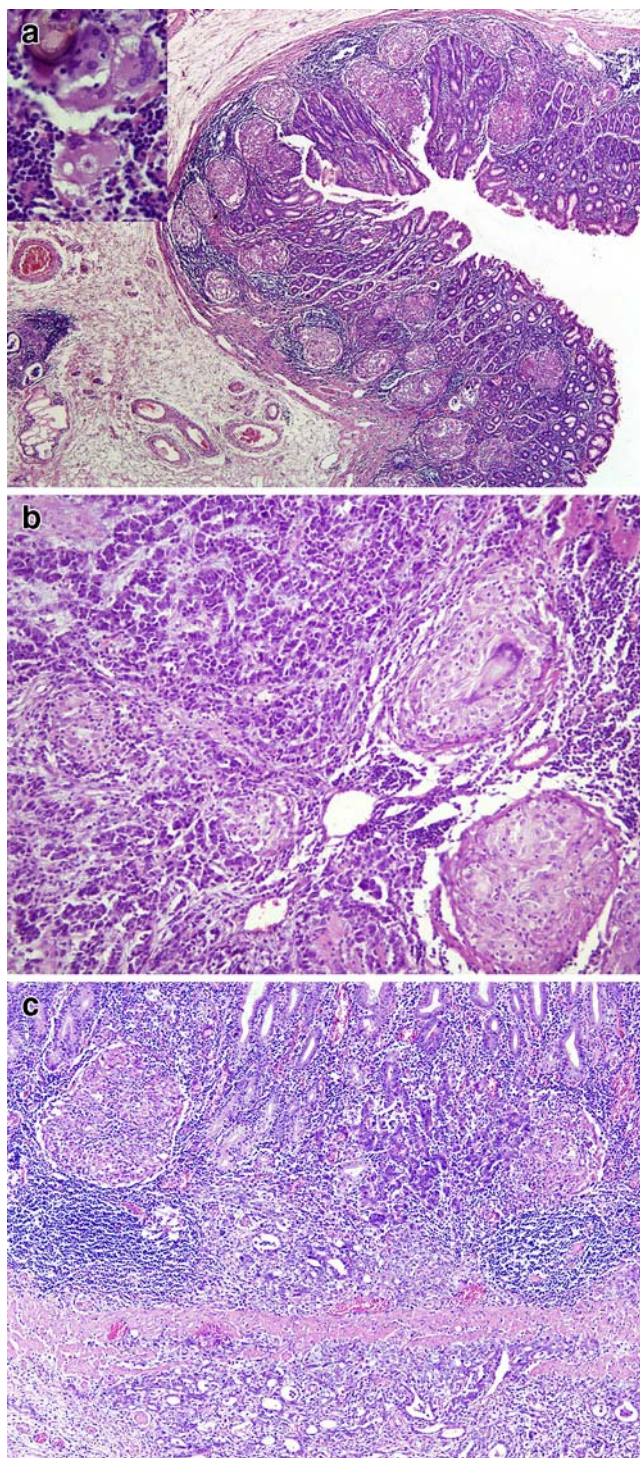


Fig. 2 Numerous sarcoid-like epithelioid cell granulomas in the uninvolved gastric mucosa (**a**), within lymph node close to the metastatic neuroendocrine component (**b**) and adjacent to the adenocarcinoma at the mucosal level (**c**). Laminated Schaumann bodies, and asteroid bodies were seen within giant cells of sarcoid-like granulomas (**a**, inset). (hematoxylin-eosin, original magnification: **a**, $\times 12,5$; **a** inset, $\times 1000$; **b**, $\times 200$; **c**, $\times 100$)

Discussion

In the stomach, mixed tumors of glandular and neuroendocrine cells have been documented as a part of a wide histological spectrum. In the literature, the definition of MEEC and the distinguishing criteria from carcinomas with NE differentiation are not uniform: some authors take into account the amount of the NE component only, while others consider type and the extent of the observed morphological pattern [1, 2]. In 1987 Lewin [4] proposed a simple nomenclature for gastrointestinal adenocarcinomas with endocrine differentiation and divided these neoplasms into three groups: (a) mixed, or composite glandular-endocrine cell carcinomas characterized by an intricate admixture of both elements; (b) amphicrine tumors with dual differentiation occurring in the same cell; and (c) collision tumors in which endocrine component and adenocarcinomas are closely juxtaposed but not admixed. The first group, mixed glandular-endocrine carcinomas, is further subdivided into microglandular-goblet cell carcinomas and adenoendocrine cell carcinomas, well-differentiated or poorly differentiated. These tumors are classified as truly mixed—composite only if both components are present in significant proportions; i.e. endocrine cells must comprise at least one third to one half of an adenocarcinoma. Sometimes it is difficult to decide whether the tumor is truly a single neoplasm that has differentiated into two directions (a composite tumor), or whether the tumor is composed of two separate neoplasms that have coincidentally arisen next to each another (collision tumor) [4, 6]. According to Capella et al. [7], gastric epithelial tumors composed of exocrine and endocrine cells can be divided into two broad groups: 1. adenomas or adenocarcinomas with interspersed endocrine cells and 2. mixed exocrine-endocrine tumors, in which the endocrine component represents at least one-third to half of the tumor tissue. The latter group is subdivided into: a) combined tumors in which the two components intermingle and seem to merge together; and b) composite tumors in which the two components occur mainly as separate areas, although close to each other, in the same neoplasm. Collision tumors are regarded, by the same group of authors [14], as double tumors composed of two topographically clearly separated components, existing next to each other coincidentally, and by definition are not included in the category of mixed tumors.

According to Volante et al. [1, 2], no reasonable explanation is provided for the currently used limit of the endocrine component extent of 30%, because the morphological criterion is essential for the definition of MEEC, as those tumors with a well-represented endocrine component are easily recognized as such. The criterion of the structural pattern in the definition of MEEC is relevant to allow separation from conventional adenocarcinoma with the less

Table 1 Immunohistochemical features of the composite carcinoma of the stomach

| Antibodies | Growth pattern | | |
|-------------------------|--------------------|-------|---------------------|
| | Exocrine component | | Endocrine component |
| | WD | PD | |
| Pancytokeratin | +++ | +++ | +++ |
| CK7 | +++ | +++ | - |
| CK20 | +++ | - | - |
| CEA | +++ | ++ | ++ |
| Chromogranin A | +s | - | ++ |
| Synaptophysin | +s | - | +++ |
| NSE | +s | - | +++ |
| Gastrin | - | - | - |
| Somatostatin | - | - | - |
| Serotonin | - | - | - |
| Glucagon | - | - | - |
| Insulin | - | - | - |
| Ki-67 (labelling index) | 47% | 50.5% | 60.5% |

(-) no immunostaining; (+) <10% cells stained; (++) 10-50% cells stained; (+++) >50% cells stained

CK cytokeratin, CEA carcinoembryonic antigen, NSE neuron-specific enolase, WD well-differentiated, PD poorly differentiated, s scattered positive cells within neoplastic glands

pronounced NE cell population randomly spread in the exocrine tumor, in the absence of carcinoid-like or small-cell areas. These carcinomas containing NE cells that represent less than one-third of the entire tumor cell population and, more frequently, when scattered in an otherwise dominant glandular growth pattern, are regarded as (adeno) carcinomas with focal NE differentiation. Volante et al. [1, 2] do not include conventional adenocarcinomas with focal NE differentiation into MEEC, because the amount of endocrine cells is variable in these tumors and depends on the immunohistochemical markers used to identify such NE differentiation, and on the number of specimens examined, all of which make the 30% cutoff-rule ambiguous. Consequently, only two major morphological patterns in mixed exocrine-endocrine neoplasms are encountered: 1. goblet cell carcinoid and 2. MEEC containing frankly glandular areas intermingled with typical NE areas (well-differentiated tumor) or with the classical small cell carcinoma areas, both being clearly distinguishable by the morphology [2].

Our case, designated either as composite [1, 2, 4–6] or combined [7] tumor, fulfills the criteria of a true mixed exocrine-endocrine tumor, exhibiting the endocrine component in a significant proportion, according to the “rule of 30%” of Lewin [4], and the structural, morphologically recognizable, pattern with typical NE areas [2].

According to Capella et al. [7] some 30 cases of mixed adenocarcinoma-carcinoid composite tumors and approximately 40 cases of mixed tumors with poorly differentiated endocrine (small cell) carcinoma have been described within

the gastrointestinal tract prior to 2000. With regard to the gastric location, Yang et Rotterdam [5] in 1991 reported one case of mixed carcinoid-adenocarcinoma of the stomach and reviewed 20 documented cases previously described in the literature. Since 1991, 30 cases of composite exocrine-endocrine carcinomas of the stomach have been published [15–27]. In addition, 21 composite carcinomas were only briefly described in a series of gastric NE carcinomas [9] without the description of the exact amount of the components. The majority of published mixed-composite gastric tumors consisted of well-differentiated or signet ring cell carcinoma in combination with carcinoid, goblet cell carcinoid or well differentiated endocrine carcinoma [15, 17–20, 23–27]. Composite gastric carcinomas with poorly differentiated endocrine component have been reported in 12 cases thus far [16, 18, 21, 22]; these tumors displayed exocrine component as well-differentiated intestinal adenocarcinoma in seven cases [16, 21], poorly differentiated tubular—intestinal type adenocarcinoma in three cases [16, 22] and signet ring cell carcinoma in two cases [18]. Accordingly, the present tumor is the fourth reported composite gastric carcinoma in which both components were poorly differentiated, containing predominantly poorly differentiated tubular/intestinal adenocarcinoma, and small cell NE carcinoma.

Immunohistochemistry confirmed the exocrine and NE nature of the tumor components, with the expression of cytokeratins and CEA in the adenocarcinomatous component and the NE markers in endocrine tumor areas. CEA was also positive in the NE component, the finding seen also in a part

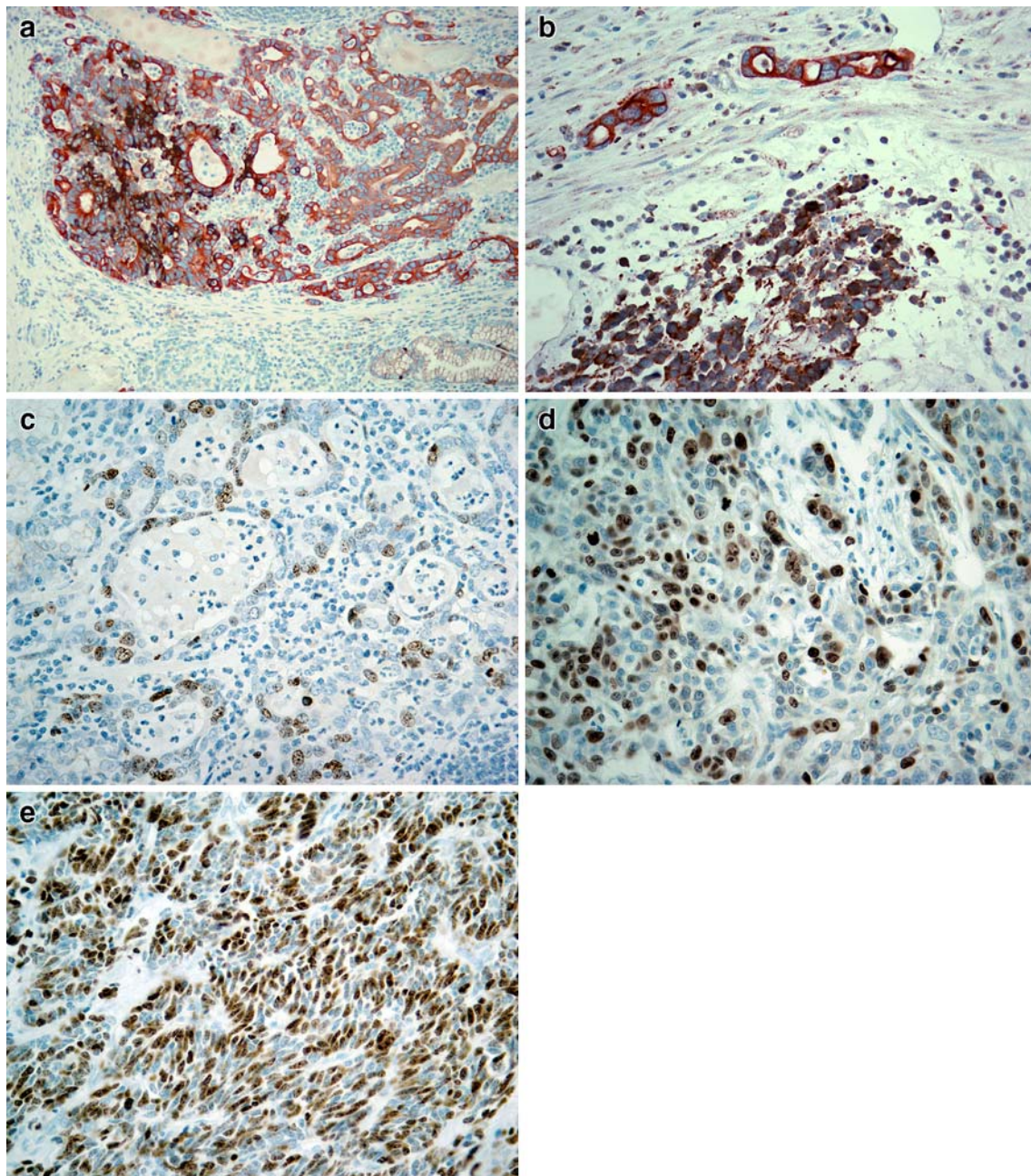


Fig. 3 Immunohistochemical double staining depicts CK7-positive neoplastic glands (red) with increased number of chromogranin A-positive neuroendocrine cells (*dark-brown*) (**a**); adenocarcinomatous component positive for CK7 (*red*) and neuroendocrine component positive for synaptophysin (*brown*) (**b**) (streptavidin-biotin double staining with diaminobenzidine [DAB] and aminoethylcarbazole

[AEC] chromogens, original magnification: **a**, $\times 200$; **b**, $\times 400$); Ki-67 immunostaining shows many positive cells in well-differentiated (**c**) and poorly differentiated (**d**) adenocarcinomatous component, and in the neuroendocrine component (**e**) (streptavidin-biotin, original magnification: **c**, **d**, **e**, $\times 400$)

of NE gastric carcinomas of Matsui et al. [9]. Scattered cells in well-differentiated glandular component were also positive for all pan-endocrine markers, which is in agreement with previous reports [3, 16, 28]. The NE component was immunonegative for all hormonal peptides, similarly to the frequent lack of hormonal expression in gastrointestinal small cell carcinomas [5, 7, 22, 29]. The mitotic rate in small

cell NE component ranges from 10 to 80 mitotic figures/10 HPFs [7], and 18 and 46 mitoses/10 HPFs were found in well-differentiated NE portions of two composite carcinomas [18]. The data regarding Ki-67 LI of the composite tumors are scarce: in the signet ring cell component of a composite tumor of Nugent et al. [19] Ki-67 LI was $>70\%$, while it was $<2\%$ in the NE component consisting of “malignant

carcinoid". In three composite glandular and endocrine tumors with pancreatic acinar differentiation, the immunostaining with Mib-1 antibody revealed positivity in about 10% of cells [15]. A Ki-67 LI value >20% has been recently proposed for diagnosing poorly differentiated, G3 NE carcinoma of the gastrointestinal tract and pancreas [29], and this percentage was exceeded by Ki-67 LI of 60,5% in the NE component of our case.

The histogenesis of composite tumors has not been fully explained. Most authors favor the theory of a monoclonal origin of the two components from the pluripotent epithelial stem cell that undergoes a biphenotypic differentiation after the initiation of carcinogenesis [5, 7, 14, 18, 19]. Alternatively, it has been suggested that most composite gastric carcinomas sequentially evolve from an adenocarcinoma/glandular precursor cell (an early-stage adenocarcinoma) to a genetically heterogeneous adenocarcinoma and then to NE carcinoma, while occasional tumors arise from a pluripotent epithelial cell [10, 16, 28]. The clinical behavior of composite carcinomas depends on adenocarcinomatous component if associated endocrine component is well-differentiated, and upon the NE component if it is poorly differentiated [1].

The present case of composite gastric carcinoma was associated with numerous non-caseating epithelioid cell granulomas, observed close to the tumor tissue and extensively in the noninvolved gastric mucosa, as well as within all perigastric lymph nodes. Since no pulmonary, skin or ocular lesions indicative of systemic sarcoidosis were seen in this patient, a diagnosis of composite exocrine-endocrine gastric carcinoma associated with sarcoid reaction was established. It has been suggested that sarcoid reactions may be caused by soluble antigenic factors derived from tumor cells [30]. Sarcoid reaction might be a marker of an immunologically mediated anti-tumor response of macrophages activated by T lymphocytes that may influence longer survival [30]. The possibility of associated Crohn's disease was excluded due to the absence of other characteristic features, except granulomas: "cobblestone" mucosa, wall stiffness, luminal stenosis and histologically—submucosal edema and fibrosis with lymphangiectasia, transmural chronic inflammation with lymphoid aggregates, fissuring ulcers, and neuronal hyperplasia [31]. The patient also lacked perianal and terminal ileum involvement.

To the best of our knowledge, there have been no previous reports regarding an association between sarcoid reaction and composite exocrine-endocrine carcinoma of the stomach.

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