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Scirrhous Endocrine Cell Carcinoma of the Stomach with Synchronous Production of Six Polypeptide Hormones and Glycoproteins. A Case Report.

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ABSTRACT

A case of scirrhous endocrine cell carcinoma of the stomach in a twenty-nine-year-old man was reported. Histologically, the tumor showing poorly differentiated adenocarcinoma with dense stromal fibrosis, was composed predominantly of tumor cells demonstrating positive argyrophil reaction by Grimelius staining. Immunohistochemically, they revealed the immunoreactivities to gastrin, somatostatin, glucagon, glicentin, pancreatic polypeptide and calcitonin in variable degree. Moreover, synchronous production of carcinoembryonic antigen (CEA), secretory component, lysozyme and mucin were also demonstrated. In view of the multidirectional differentiation, the scirrhous endocrine cell carcinoma might be derived from totipotent stem cell of endodermal origin.

In 1927 Hamperl[5] reported that argentaffin or argyrophil cells were present in ordinary carcinoma of the gastrointestinal tract. Since then it has been confirmed by many investigators[2,7,13,14]. We have recently reported gastric scirrhous carcinomas with numerous argyrophil or argentaffin cells, and named them as "scirrhous argyrophil or endocrine cell carcinoma" of the stomach[15,16].

In this paper, we report a case of scirrhous endocrine cell carcinoma of the stomach, which developed in a young male and showed positive immunoreactivities to six polypeptide hormones, CEA and lysozyme synchronously. The histogenesis of the endocrine cell carcinoma will be also discussed.

CASE REPORT

Clinical History

A twenty-nine-year-old man was admitted to the Department of Surgery, Research Institute for Nuclear Medicine and Biology, Hiroshima University because of epigastralgia over two years. Rentogenographic examination revealed a tumor with central ulceration at lesser curvature of the gastric body. Poorly differentiated adenocarcinoma was detected by endoscopic gastric biopsy, and subtotal antral gastrectomy was performed. The operation was successful and no metastasis was presented in the regional lymph nodes. After the operation, he has been well for eight years without any signs of recurrence or metastasis. Before and after the operation, no overt endocrine syndrome was observed.

Pathological Findings

Macroscopically, the tumor was located anterior to the lesser curvature line in the body of the stomach, measuring 5.5 × 2.5 cm in size with a small central ulceration, corresponding to IIc like advanced type (Fig. 1). On cut surfaces, it showed downward invasion into the subserosa.

The resected stomach was fixed in 10% neutral buffered formalin, and embedded in paraffin. Serial 4 μm in thickness sections from the representative blocks were stained with hematoxylin and eosin, periodic-acid-Sciff(PAS)-

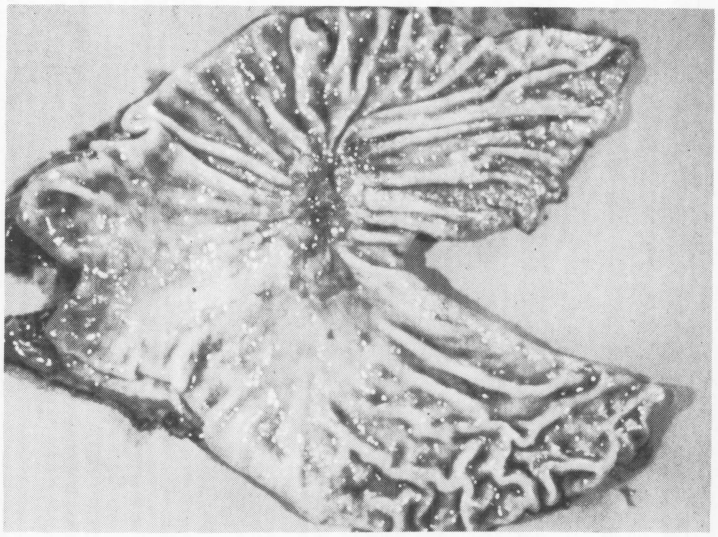

Fig. 1. Gross appearance of the resected stomach, showing ulcerative tumor lesion in the gastric body

alcian blue, Grimelius technique for argyrophil reaction and Fontana-Masson technique for argentaffin reaction. The tumor consisted of poorly differentiated adenocarcinoma with dense stromal fibrosis and invaded into the subserosal tissue on the sections stained with hematoxylin and eosin. Each tumor cells has relatively abundant eosinophilic, fine granular cytoplasm (Fig. 2a). Most of these tumor cells showed argyrophilia with Grimelius reaction (Fig. 2b). A few of signet ring cells, which were positive with alcian blue stain, were also observed in the tumor tissue (Fig. 2c).

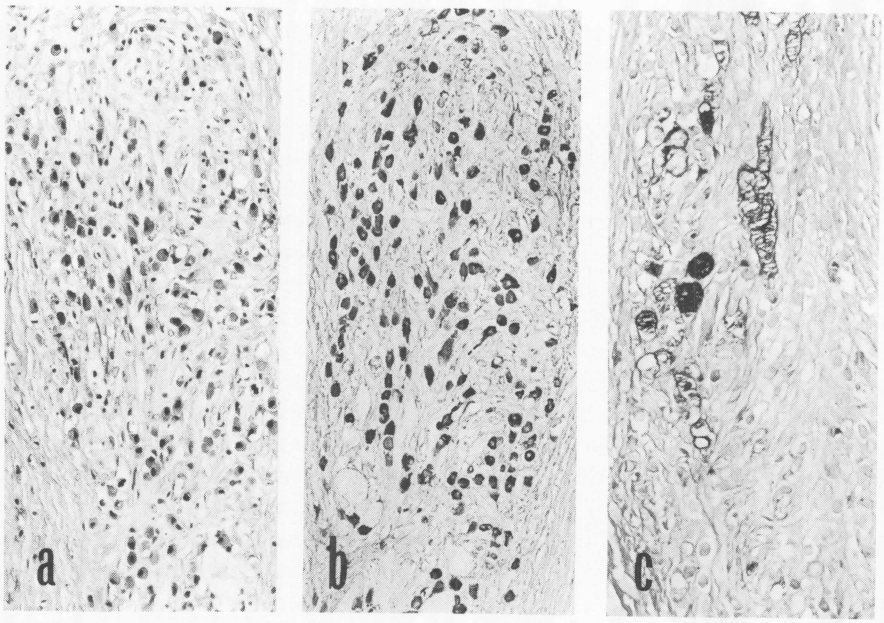

Fig. 2a-c. Photomicrograph of the tumor. **a** Hematoxylin and eosin (×160). Poorly differentiated adenocarcinoma with diffuse fibrosis. **b** Grimelius' silver impregnation (×160). Most of the tumor cells show diffuse argyrophilia. **c** Periodic-acid-Schiff-alcian blue stain (×160). Alcian blue positive signet ring cells are scattered in the tumor tissue

Table 1. List of primary specific antisera and immunohistochemical findings

Antisera to	Source	Dilution	Immunoreactivity[a]
Gastrin	from ex-Prof. A. Miyoshi (Hiroshima, Japan)	1:200	++
Glicentin	from Prof. N. Yanaihara (Shizuoka, Japan)	1:800	+++
Glucagon	Japan Immunoresearch Lab. Co., Ltd. (Takasaki, Japan)	1:150	+++
Somatostatin			+
Pancreatic polypeptide			++
Calcitonin	Dakopatts A/C (Copenhagen, Denmark)	1:400	+++
Carcinoembryonic antigen			+++
Secretory component			++
Lactoferrin			−
Lysozyme			++
α-1-Antitrypsin			−
α-Fetoprotein			−
hCG-β subunit	Bioactive Chemicals Lab., Ltd. (Tokyo, Japan)	1:200	−

[a] These reactions are graded +, ++ and +++ on the basis of the frequency of staining of individual cells

A modification of the immunoglobulin enzyme bridge technique was employed as described in detail by Tahara et al[15]. Primary specific antisera used in this study were listed and immunohistochemical findings were summarized in Table 1. Antirabbit IgG was purchased by MBL Co. (Nagoya, Japan), and soluble peroxidase antiperoxidase complex were obtained from Dakopatts A/C (Copenhagen, Denmark). Immunohistochemically, more than twenty five percent of tumor cells showed intense positive reaction to gastrin, glicentin, glucagon, pancreatic polypeptide, calcitonin and CEA (Fig. 3). Under twenty five per cent of tumor cells had immunoreactive lysozyme and secretory component. Small population of the tumor cells also revealed somatostatin immunoreactivity. Any tumor cells showed no positive reaction to lactoferrin, α-1-antitrypsin, α-fetoprotein, and hCG.

DISCUSSION

It has been reported that there exsist tumors showing neuroendocrine differentiation among gastric adenocarcinoma[2,3,6,11]. We have proposed following two criteria for such "endocrine cell carcinoma of the stomach": (1) the vast majority of carcinoma cells were of endocrine cells showing a positive reaction for the Grimelius stain, and (2) these endocrine cells were present in a diffuse distribution throughout the tumor tissue. According to these criteria, endocrine cell carcinomas were found in about 30% of scirrhous carcinoma of the stomach[15,16].

The present case which was a scirrhous gastric carcinoma fulfilled these criteria completely. Tumor cells contained immunoreactive gastrin, glicentin, glucagon, pancreatic polypeptide, calcitonin, somatostatin. They also revealed positive immunostaining for CEA, secretory component and lysozyme. Moreover, some of the tumor cells had alcian blue positive acid mucopolysaccharide. Although the expression of polypeptide hormones or glycoproteins is frequently detected in gastric adenocarcinoma, synchronous production of six polypeptide hormones in this case seems to be a rare phenomenon.

This case also suggested that endocrine cell carcinoma showing multidirectional differentiation might be derived from neoplastic totipotent stem cell of endodermal origin. Experimental studies using chick or rat embryos support this speculation, namely endocrine cells of gastrointestinal tract are endodermal origin[1,8,10] and they are differentiated and regenerated from totipotent epithelial stem cells together with mucous, parietal and chief cells[9].

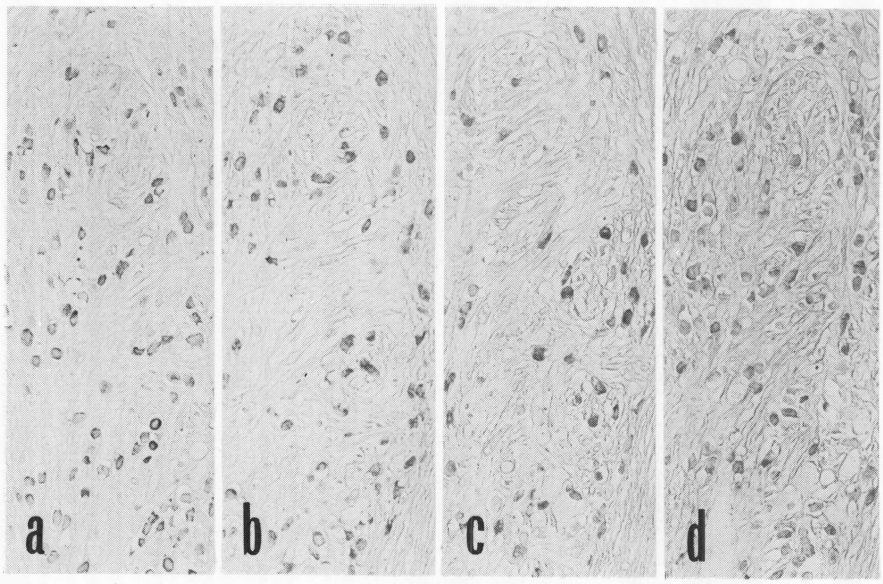

Fig. 3a-b. Immunohistochemical findings of the endocrine cell carcinoma. A good number of tumor cells show gastrin (**a**), glicentin (**b**), glucagon (**c**) and also calcitonin (**d**) immunoreactivity. Immunostaining with PAP method (×160).

It is also suspected that multihormonality of endocrine cell carcinoma may be caused by the wide range of gene expression and altered metabolic processing system in tumor cells[4,12]. The production mechanism of multiple polypeptide hormones as well as the desmoplastic mechanism often seen in endocrine cell carcinoma of the stomach is to be elucidated in the future.

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