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Primary gastric choriocarcinoma associated with adenocarcinoma

—A Case Report with Immunohistochemical Study—

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Abstract A case of a 69 year old female with primary gastric choriocarcinoma was presented with special reference to histogenesis by using the immunohistochemical technique (PAP method). The gastric tumor in this case was histologically diagnosed as choriocarcinoma coexistent with adenocarcinoma. From hormonal standpoint, the diagnosis was confirmed by recognition of high HCG titers in both the serum and tumor. The primary focus of the choriocarcinoma was detected neither in the genitourinary tract nor in the mediastinum in spite of a thorough autopsy. By PAP method tumor cells of choriocarcinoma showed high positive reaction only to anti-HCG antiserum and less positive to anti-HPL and SP1 antisera in contrast to those of uterine choriocarcinoma with high positive reaction to anti-HCG, HPL and SP1 antisera. Tumor cells of adenocarcinoma showed positivity to anti-CEA and anti-AFP antisera by the same method. These results indicate that gastric choriocarcinoma might be functionally different from gestational choriocarcinoma. Moreover, tumor cells of adenocarcinomatous lesion have some resemblance to embryonal carcinoma morphologically and immunohistochemically. Therefore, the origin of gastric choriocarcinoma seemed to be morphological retrodifferentiation of tumor cells to embryonal ectoderm such as trophoblastic cells.

Ker Words: choriocarcinoma, adenocarcinoma, stomach, immuoohistochemistry, histogenesis

Introduction

Choriocarcinoma is a highly malignant tumor arising from trophoblastic cells of the uterus associated with normal gestation or with molar pregnancy. Ectopic choriocarcinoma is detected in the gonads and the midline tissues (mediastinum, retroperitone-

um, and pineal body) with lesser frequency, usually as a part of teratomatous lesions. In the rare case the ectopic choriocarcinoma may originate in the gastrointestinal tract [1-4].

In this paper, a case of primary gastric choriocarcinoma coexistent with adenocarcinoma was reported to present the histogenesis of this neoplasm by the method of immunoperoxidase technique, using antisera to human chorionic gonadotropin (HCG) and other pregnancy-specific proteins (HPL, SP1), carcinoembryonic antigen (CEA) and α-fetoprotein (AFP).

A case report

A 69-year-old female was admitted to Yamaguchi Central Hospital with complaints of general fatigue and tarry stool. Pursuing the cause of the bleeding, a gastric fluoroscopy demonstrated a large irregular cancerous lesion at the antrum. Endoscopic examination of the stomach revealed a protruded lesion on the anterior wall of the antrum. The center of lesion was covered with bloody coagula. Biopsy specimen from the margin of the lesion was histologically diagnosed as tubular adenocarcinoma. Laboratory examination showed hemoglobin of 5.2 g/dl, hematocrit of 18.2%, serum protein of 6.2 g/dl, serum LDH of 114 WU, serum alkaline phosphatase of 6.2 KAU and choline esterase of 0.94 △pH. Three weeks after hospitalization subtotal gastrectomy and cholecystectomy were carried out because a gall bladder carcinoma was found at operation. The stomach contained a large protruded tumor at the antrum. Gastric specimen was histologically diagnosed as choriocarcinoma coexistent with tubular adenocarcinoma. Postoperative serum HCG level was 8,000 mIU. Thereafter, the HCG level was elevated slowly in spite of intensive chemotherapy with methotrexate and cyclophosphamide. Metastatic lesions to the liver, demonstrated by CT scan, enlarged rapidly. About 6 months after operation she expired, and autopsy was performed. Laboratory data including hormone titers were shown in Table 1 and Fig. 1.

Table 1 LABORATORY DATA THROUGH CLINICAL COURSE

	1982 27, Mar,	17, May	10, Jun.	29, Jun.	20, Jul.	19, Aug.	5, Oct.	2, Nov.
RBC ($\times 10^4$/mm^3)	187	414	415	423	358	342	383	498
Hb (g/dl)	5.2	11.1	11.7	12.3	10.7	10.3	12.0	15.0
GOT (0-40 KU)	17	Transfusion	248	123	22	34	33	3500↑
GPT (0-35 KU)	12	20	173	134	15	18	13	443
ALP (2.7-10KA)	6.2	13	12.9	12.1	8.6	6.8	12.2	4.5
LDH (60-140 WU)	114	5.4	205	174	148	123	380	2000→
Ch. E. (0.7-1.1 △pH)	0.94	153	0.75	0.80	0.54	0.56	0.69	0.37
CEA-Z (0-5.0 ng/ml)		0.75	2.2				6.6	
T. Cholesterol (130-230 mg/ml)	209	166	180	163	187	204	167	36
Serum Estrogen (E_1: 5-40ng/ml)			149		134		858	
HPL (g/ml)			0.25↓					

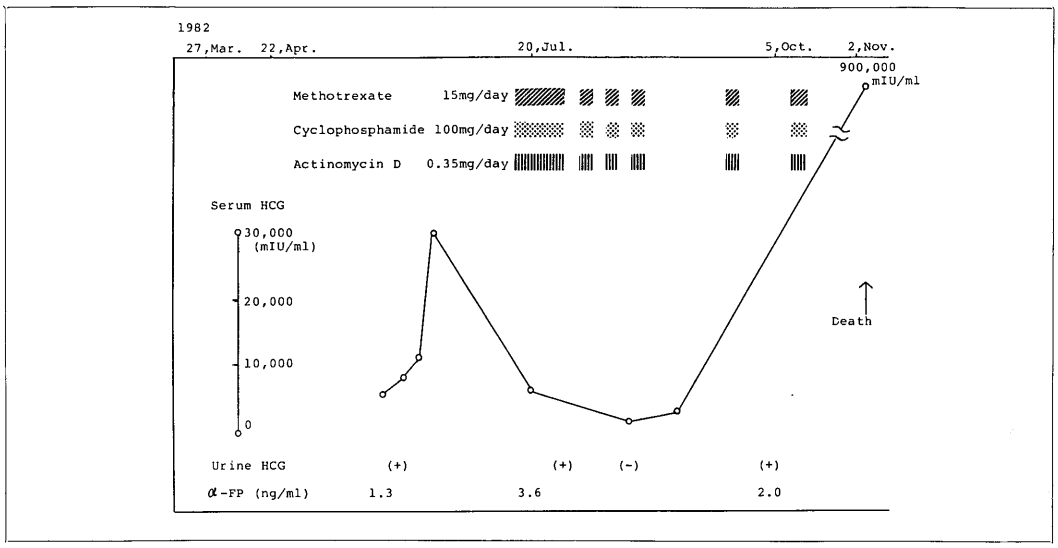

Fig. 1 Available drugs and laboratory data on hormone titers during the clinical course of this case.

Materials and Methods

Several tissues taken from the patient at the time of the operation and necropsy were examined histologically using standard techniques. Tissue sections were stained with hematoxylin-eosin. The unlabeled immunoperoxidase method (PAP method) was also applied to these tissue sections as follows; PAP Method.

a. Antisera: Anti-human HCG (β-HCG), anti-human placental lactogen (HPL), anti-pregnancy-specific α-1 glycoprotein (SP1), anti-human carcinoembryonic antigen (CEA) and anti-human α-fetoprotein (AFP) antisera obtained from DAKO (Copenhagen, Denmark) were used in this study.

b. Methods: Sternberger's PAP method[5] was used with a minor modification.

c. Reagents: Normal goat serum, normal rabbit serum, goat anti-rabbit IgG, and peroxidase-antiperoxidase (rabbit, PAP) were obtained from DAKO (Copenhagen, Denmark).

d. Control Study: Anti-human HCG antiserum and other antisera were replaced by the same dilution of normal serum. And then control tissue sections such as 3 cases of uterine choriocarcinoma, 5 cases of hydatidiform mole, and 5 cases of normal placental tissue were prepared for the PAP method using antisera to human HCG and other antisera.

HCG titer of tumor tissue, obtained from metastatic lesions of choriocarcinoma to the liver at necropsy, was determined by radioimmunoassay.

Results

A. Surgical Specimens:

Macroscopic Findings; At operation an ulcerated tumor was found in the anterior wall of the antrum (Fig. 2). A cut surface of the tumor exhibited a highly hemorrhagic lesion with partial necrosis. The remaining gastric mucosa showed no remarkable change.

Microscopic Findings; The tumor consisted of two elements. One was a choriocarcinoma occupying the center of tumor, and the other was adenocarcinoma occupying the periphery. Choriocarcinoma was composed of predominant large polygonal cells with clear cytoplasms arranged in sheets and multinucleated cells with amphophilic cytoplasms (Fig. 3). The former seemed to be cytotro-

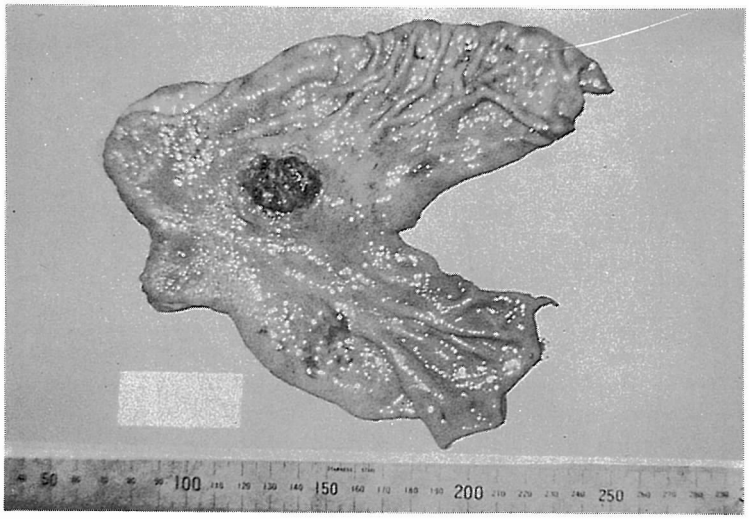

Fig. 2 Macroscopic finding of the resected stomach. Tumor mass with hemorrahagic ulcer is found in the anterior wall of the antrum.

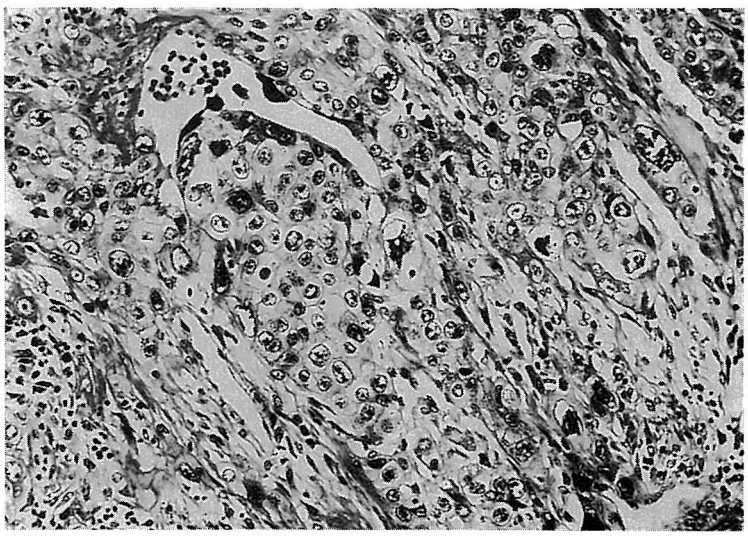

Fig. 3 Choriocarcinomatous lesion is mainly composed of large cells with clear cytoplasm consistent with cytotrophoblasts. H.E. stain. original mag. ×100.

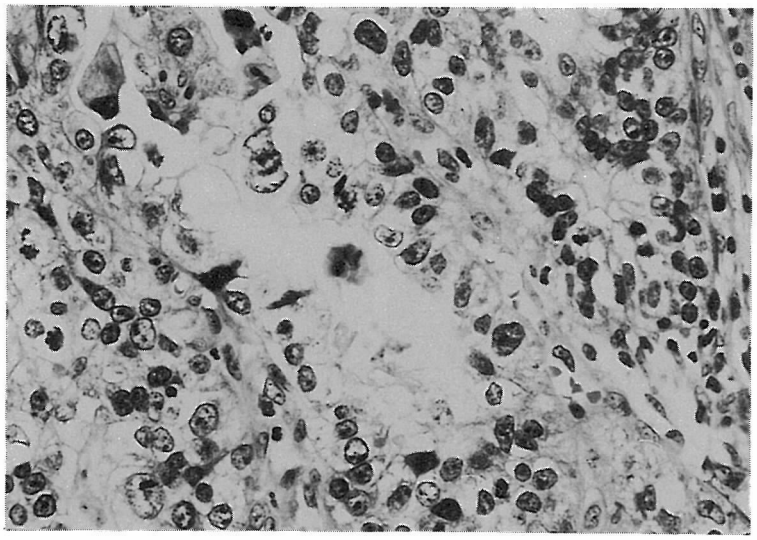

Fig. 4 Some tumor cells in the adenocacinomatous lesion are polygonal cells with clear cytoplasm. These cells have some resemblance to embryonal carcinoma in histology. H.E. stain. original mag. ×200.

phoblast, and the latter syncytiotrophoblast. The stroma of this tumor was highly vascular. Tumor cells of adenocarcinoma, which was relatively demarcated from choriocarcinomatous lesion, were polygonal cells with clear cytoplasms (Fig. 4). There was no apparent transitional form between both tumor elements. Metastasis of both choriocarcinoma and tubular adenocarcinoma to the regional lymph nodes was already observed at operation. No teratomatous elements were detected. Tumor of the gall bladder histologically showed papillary adenocarcinoma without metastasis to the regional lymph nodes.

Immunoperoxidase technique was applied to the tissue sections of the stomach. Tumor cells of choriocarcinoma showed high positivity to anti-HCG antiserum in PAP method (Figs. 5a, 5b). The positive reaction was shown in most of large tumor cells with amphophilic cytoplasms, resembling syncytiotrophoblast. The positive reaction was also detected in some of large clear cells, similar to cytotrophoblast. No tumor cell of adenocarcinoma showed positive staining to anti-HCG. Tumor cells of adenocarcinoma, on the contrary, showed positive staining to anti-CEA and anti-AFP antisera (Figs. 6a, 6b). The serial sections of gastric mucosa have less positivity to anti-HPL and anti-SP1. On the other hand, control studies using the same antisera showed positivity in trophoblastic cells of normal placenta, hydatidiform mole and tumor cells of uterine choriocarcinoma.

B. Autopsy Findings:

Metastatic tumors were predominantly found in the liver, and the hepatic parenchymal cells were remarkably atrophic due to the compression by tumor masses. Metastatic lesions were also found in both lungs and the para-aortic lymph nodes. These lesions were histologically composed of solely choriocarcinomatous element with severe hemorrhage. The ovaries were slightly atrophic, showing no evidence of hilus cell hyperplasia and stromal lutenization. The uterus was remarkably large in size, and

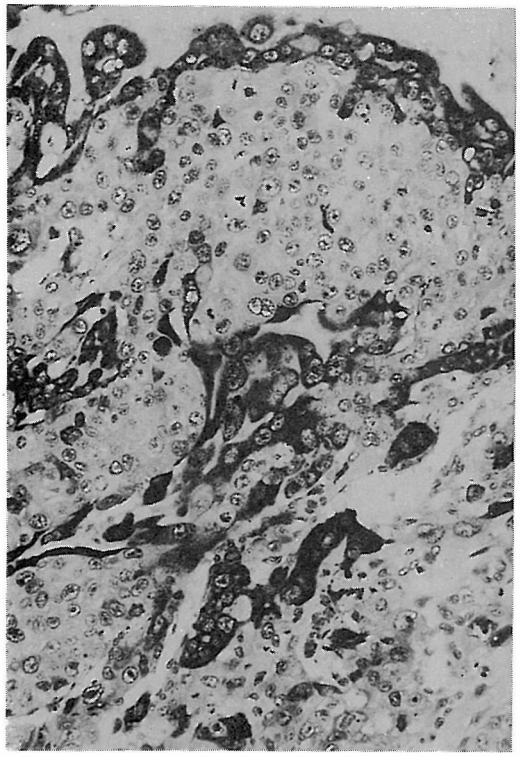

Fig. 5a Tumor cells in the choriocarcino matous lesion reveal high positivity to anti-HCG antiserum in PAP method. This reaction is shown in large tumor cells with amphophilic cytoplasm, which are regarded as syncytiotrophoblast. Immunoperoxidase stain. original mag. ×100.

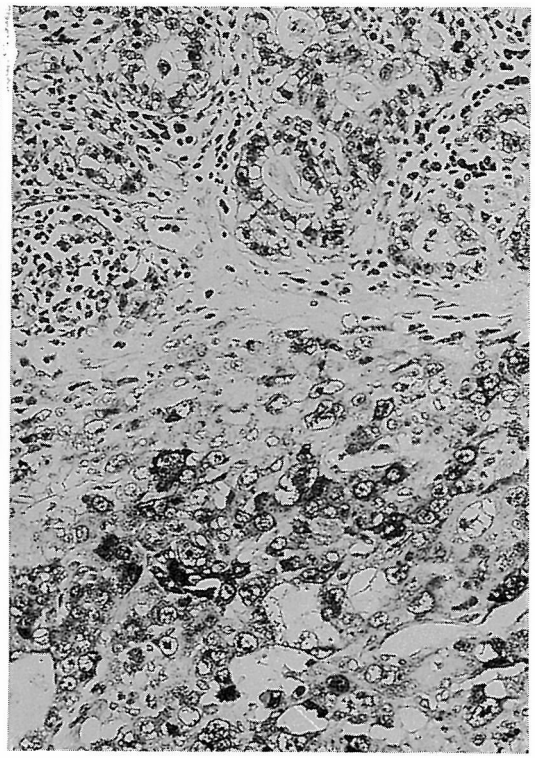

Fig. 5b Positive reaction to anti-HCG antiserum is also found in tumor cells resembling to cytotrophoblast, however, no tumor cell in adenocarcinomatous lesion have positive staining to anti-HCG. Immunoperoxidase stain. original mag. ×100.

Table 2 Cases of Gastric Choriocarcinoma in Females (Japan)

Investigators	age	location of tumor mass	coexistence of adenocarinoma	HCG (serum)
Inadomi et al. (1976)	28	corpus	(−)	none
Inadomi et al. (1976)	80	antrum	(+)	none
Ida et al. (1978)	68	unknown	(−)	(+)
Hirota et al. (1980)	55	unknown	(+)	(+)
Kudou et al. (1980)	30	pylorus	(+)	(+)
Kaijou et al. (1982)	55	antrum	(+)	(+)
Fukuda et al. (1985)	70	corpus	(+)	(+)
Our Case (1986)	69	antrum	(+)	(+)

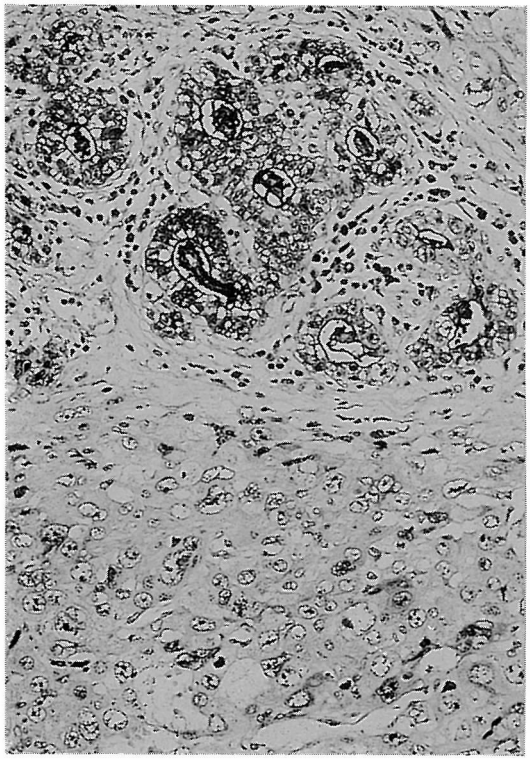

Fig. 6a Tumor cells in adenocarcinomatous lesion have positive staining to anti-CEA antiserum as usual. Immunoperoxidase stain. original mag. ×100.

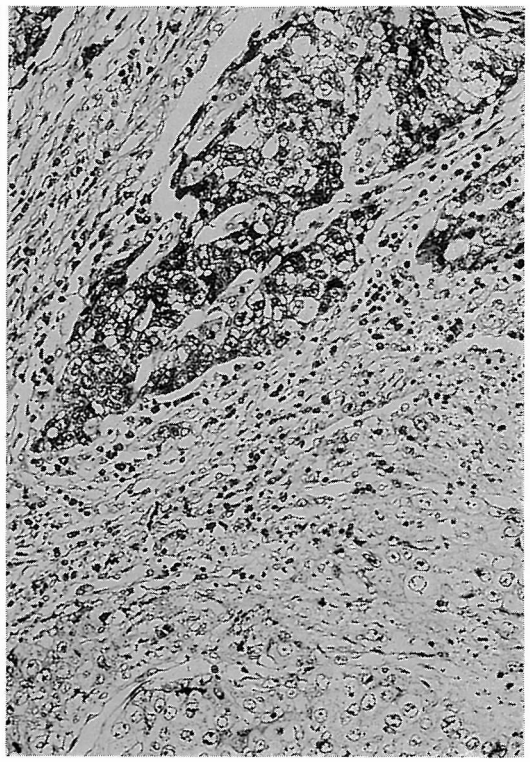

Fig. 6b Some tumor cells in adenocarcinomatous lesion showed strong positivity to anti-AFP antiserum in PAP method. Immunoperoxidase stain. original mag. ×100.

endometrium of which was remarkably hyperplastic and hemorrhagic. Endometrial glands were rather atrophic, but decidual changes of the stroma was remarkable. The mammary glands were large, and ductal hyperplasia with slight bubbling secretion was histologically proved, similar to that of gynecomastia. In serial sections of gynecological organs, there was no foci of choriocarcinoma despite detailed histological examination.

The HCG titer of tumor tissue in the liver was 7.4×10^5 mIU/g by radioimmunoassay.

Discussion

A gastric tumor in this case was diagnosed as primary gastric choriocarcinoma by typical histological features, immunohistochemical detection of HCG in the cytoplasms of tumor cells, and recognition of high HCG level in serum and tumor tissue. There have been reported 8 cases of primary gastric choriocarcinoma in females including the present case in Japan (Table. 2). In the female cases, it must be particularly careful to diagnose primary gastric choriocarcinoma. In this case, a primary lesion of choriocarcinoma was not found in genitourinary organs despite a detailed examination at autopsy. Primary choriocarcinoma of the stomach is an uncommon condition[2)3)6)]. Jindrak et al.[7)] summarized 27 cases of

primary gastric choriocarcinoma, and noted that 18 of these cases contain adenocarcinomatous component. Mori et al.[6] summarized 44 cases of gastric choriocarcinoma, and 26 cases showed a histology consisting of choriocarcinoma and other structures, particularly the adenocarcinoma. Therefore, preceding or coexistent adenocarcinoma may participate in the pathogenesis of primary gastric choriocarcinoma.

Several theories have been offered in the literature to explain the histogenesis of gastric choriocarcinoma. Davidson in 1905 postulated its origin from an abdominally displaced anlage[8]. Koritschoner postulated that the origin was a long-delayed metastasis of unproved intrauterine chorioepithelioma[9]. Voss et al. in 1954[10] suggested that the development of trophoblastic elements in a gastric adenocarcinoma was caused by the retrodifferentiation of the tumor cells of adenocarcinoma to the level of embryonal ectoderms as well as the description of Pick et al.[11] in 1926. The above mentioned explanation for the histogenesis of gastric choriocarcinoma seemed to be only a speculation. With respect to gastric choriocarcinoma, histochemical studies including hormonal function have not been described except for a few publications[12-15]. Wurzel et al.[15] reported a case of pure gastric choriocarcinoma with histological detection of HCG in tumor cells using immunoperoxidase technique. Saigo et al.[13] showed that β-HCG were localized to choriocarcinomatous portion of their case. In our study, the same technique was applied to the section of gastric tumor using antisera not only to HCG (β-HCG), but also to HPL, SP1, CEA and AFP. Choriocarcinomatous element showed the positive staining to only anti-HCG antiserum, and less positive to anti-HPL, SP1 and other antisera. Adenocarcinomatous element showed the positive staining to anti-CEA and anti-AFP antisera, and negative to anti-HCG, HPL and SP1 antisera. The positive staining to anti-HCG, anti-HPL and anti-SP1 antisera was recognized in the trophoblastic cells of normal placenta and hydatidiform mole, and tumor cells of uterine chorioepithelioma used as control in this study. Mori et al.[6] reported two cases of male gastric choriocarcinoma coexistent with adenocarcinoma using immunohistochemical study in addition to the review of the literature on gastric choriocarcinoma of 44 cases. According to their results, the PAP method for anti-HCG demonstrated the localization of HCG in the most of syncytiotrophoblasts and a small number of cytotrophoblasts which is in agreement with our results. Moreover, they found the stain for SP1 was weakly positive in adenocarcinoma of one case but not in the choriocarcinoma. They suggested a sequential process of morphological transition of the adenocarcinoma to the choriocarcinoma. In our case, however, choriocarcinomatous portion were relatively demarcated from that of adenocarcinoma, histologically and functionally. Metastatic lesions were composed of only choriocarcinomatous component as well as the report of Saigo et al.[13]

The implication of our study was that ectopic choriocarcinoma of the stomach have a morphological similarity to gestational choriocarcinoma, but might have some functional differences of hormone-producing activity to gestational one. The component of coexistent tubular adenocarcinoma have some resemblance to embryonal carcinoma because of histological characteristics and its hormone-producing capability such as CEA and AFP.

Therefore, there may be two possibilities on the histogenesis of gastric choriocarcinoma. One is that the primary choriocarcinoma of the stomach have the heterotopic germ cell origin as well as gonadal, mediastinal and pineal choriocarcinoma. The other is the retrodifferentiation of tumor cells of adenocarcinoma to the level of germ cell with the ability to change trophoblasts.

Fukuda et al.[12] have proposed these neoplasms might be designated as "primary gastric germ cell tumor". Recently, several investigators[16] have disclosed that HCG was produced by gastric adenocarcinoma without choriocarcinomatous lesion as well as AFP. The fact described above suggested functional retrodifferentiation of adenocarcinoma and also the possibility of morphological retrodifferentiation of the tumor cells to trophoblastic cells.

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