[原著]Streptozotocin Therapy for A Total Gastrectomized Malignant Gastrinoma

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Streptozotocin Therapy for A Total Gastrectomized Malignant Gastrinoma

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ABSTRACT

A case of malignant gastrinoma where streptozotocin was effective is reported; the course after total gastrectomy of this malignancy are discussed.

Malignant gastrinoma may continue to progress even after total gastrectomy to terminate fatally.

Angiogram, assessment of serum gastrin levels loaded with secretin, scintigram are useful indices for observation of the course.

Streptozotocin has a good effect on malignant gastrinoma, while mitomycin C, 5-fluorouracil, combined chemotherapy with 5-fluorouracil, 250mg, cyclophosphamide, 150mg, mitomycin C, 2mg and chromomycin A_3, 0.5mg, at a time twice weekly (FAMT therapy) have all proved ineffective.

It used to be considered that total gastrectomy would lead malignant gastrinoma to regression of its metastases and the case would run a favorable course because of its low malignancy. [1, 2, 3] Therefore, it was not commonly accepted that the patient with this tumor would die of their tumor after total gastrectomy. However, as long-term experience with this tumor has accumulated, those terminating fatally of the tumor even after total gastrectomy have been encountered, making it necessary to perform some adjuvant therapy in them.[4] We report a case of malignant gastrinoma treated by total gastrectomy which followed by administration of streptozotocin and discuss the course, treatment and indices of observation of the course of this tumor after total gastrectomy.

CASE REPORT

A 42-year-old woman came to the hospital with a history of 8 episodes of hematemesis and melena during four months. The physical examination on admission disclosed anemia only. The bowel movement was normal. Subtotal gastrectomy was performed for duodenal ulcer on March 9, 1973. At operation, a shallow ulcer 7 x 2mm in size was found in the pyloric region.

No abnormalities were found in the liver. An episode of massive hematemesis and melena occurred on the 7th postoperative day. At re-laparotomy on March 17, 1973, a firm mass, about 3cm in diameter, was found in the tail of the pancreas. For suspected malignant gastrinoma, total gastrectomy and combined resection of the tail of the pancreas and the spleen were performed.

Microscopic examination revealed non-Beta islet cell carcinoma of the pancreas with deposits in adjacent lymph nodes (Fig. 1).

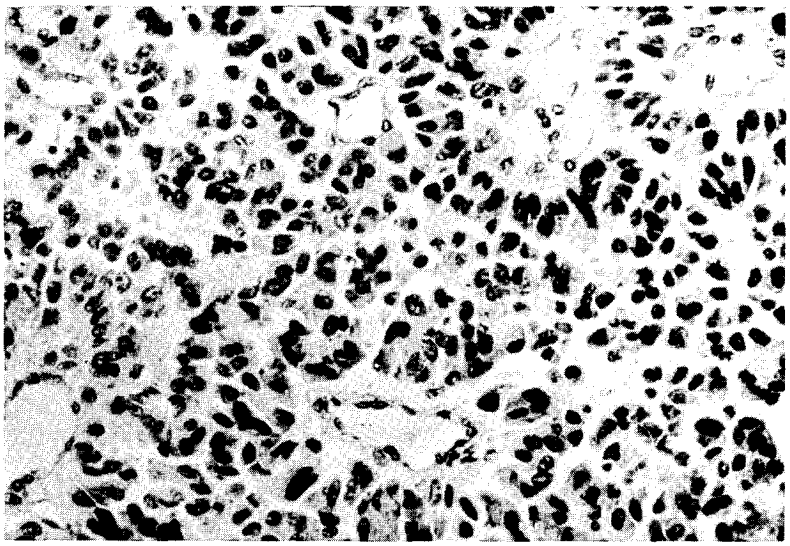

Fig. 1 Light microscopic picture from the surgical specimen showing a metastatic carcinoma in the lymphnode. The majority of the cells in the solid part of the tumor show polyhedral clear cytoplasm and round or ovoid nucleus. (H & E)

Postoperative follow-up study without anticancer treatment was made for two months. Selective angiography of the celiac artery and the superior mesenteric artery 1 and 2 months after the operation revealed several large, round, hypervascular metastatic tumors in both lobes of the liver, which were growing rapidly.

The fasting serum gastrin level was as high as 425 and 625pg/ml one and two months after the operation, respectively. Assessment of the serum gastrin levels with loading beef, glycine, calcium and secretin were performed and no explicit response was observed to beef, while the serum gastrin level increased with glycine, calcium and secretin (Figs. 2, 3 and 4).

Of the other parameters of the endocrine system , the serum serotonin, growth hormone, insulin, cortisol (11-OHCS) and calcium, the urine 17KS and 17OHCS all remained within normal range.

Three injections each of mitomycin C (MMC), 20mg, into the celiac artery, one injection of 5-fluorouracil (5-FU), 250mg, into the celiac artery, combined chemotherapy with 5-FU, 250mg, cyclophosphamide, 150mg, MMC, 2mg, and chromomycin A_3, 0.5mg, at a time twice weekly (FAMT therapy) to 30 applications in total and daily administration of 250mg of 5-FU over 63 days all proved ineffective.

Her general condition deteriorated gradually to the extent that the patient was unable to sit up one year after the operation, presenting fecal and urinary incontinences and obscure speech.

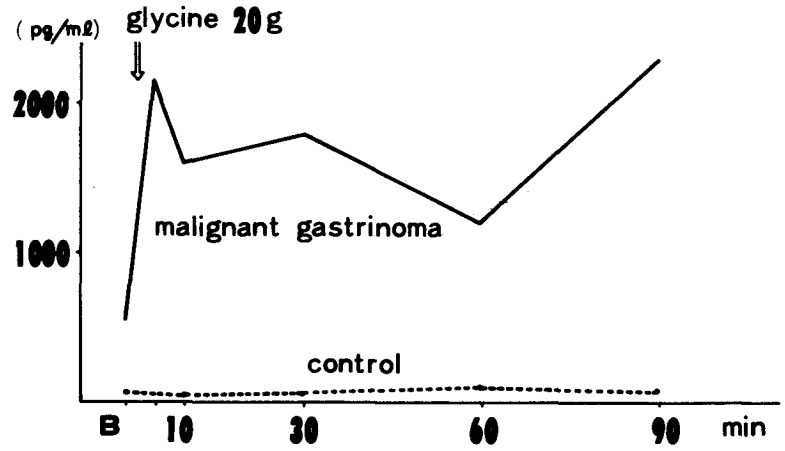

Fig. 2 Serum gastrin levels in basal condition and after oral administration of glycine 20g: after loading with glycine, serum gastrin level is increased in this case, while that in the control varies within normal range.

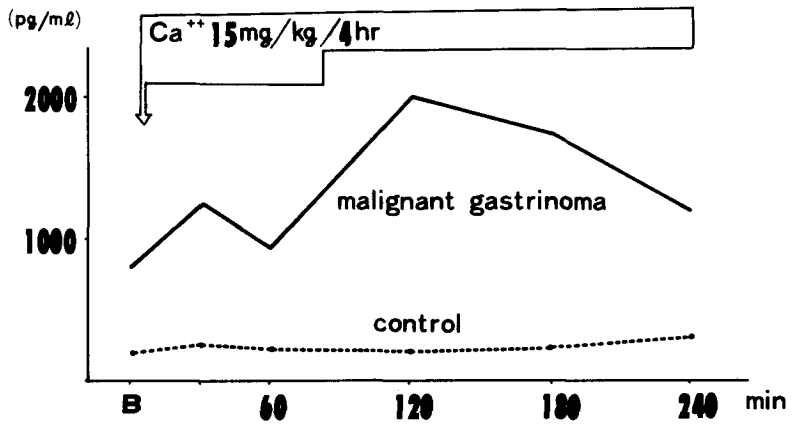

Fig. 3 Serum gastrin levels in basal condition and after calcium infusion (15mg Ca^{++}/Kg body weight) : after calcium infusion, serum gastrin level is apparently increased in this case, while that in the control varies only within normal range.

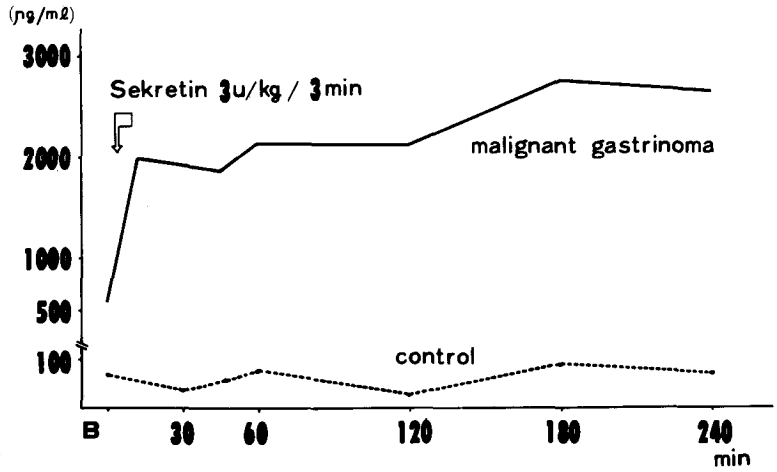

Fig. 4 Serum gastrin levels in basal condition and after secretin injection (3 Units/kg body weight) : after secretin injection, the serum gastrin level is apparently increased in this case, while that in the control varies within normal range.

At about the time, she began complaining of severe weakness and headache at fasting. Her fasting blood sugar was 36mg/dl. After an oral dose of 50g of glucose the blood sugar levels were 67 and 40mg/dl in 60 and 120 minutes, respectively. Since the fasting blood insulin was 19.5mcU/ml (normal range : 18–40mg/dl), it was judged as hypoglycemia due to the giant tumors. [5, 6] Liver had been protruded and enlarged, and the inferior margin of the right lobe reached below the umbilicus.

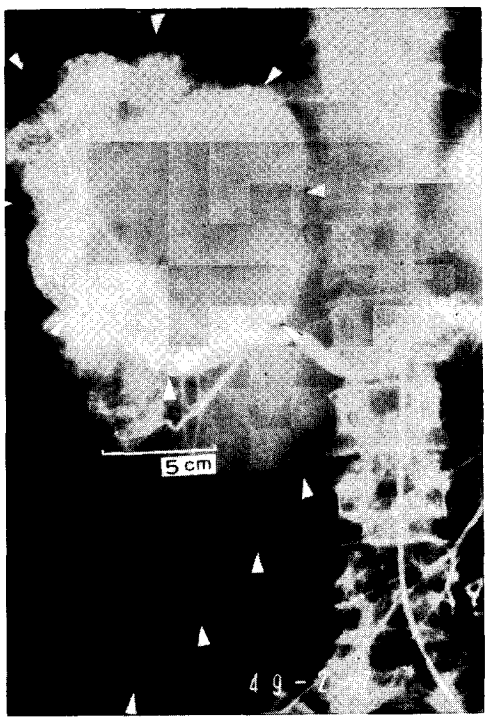

Fig. 5 Angiogram 1 year after total gastrectomy. The largest metastatic focus in the liver is surrounded with arrows. Compared with Fig. 6 the metastatic focus surrounded with arrows and the liver (the inferior margin shown with a row of arrows) have been greatly enlarged.

Figure 5 showes angiogram one year after the operation which, compared with angiogram one month after gastrectomy (Fig. 6), revealed markedly enlarged liver and liver metastases.

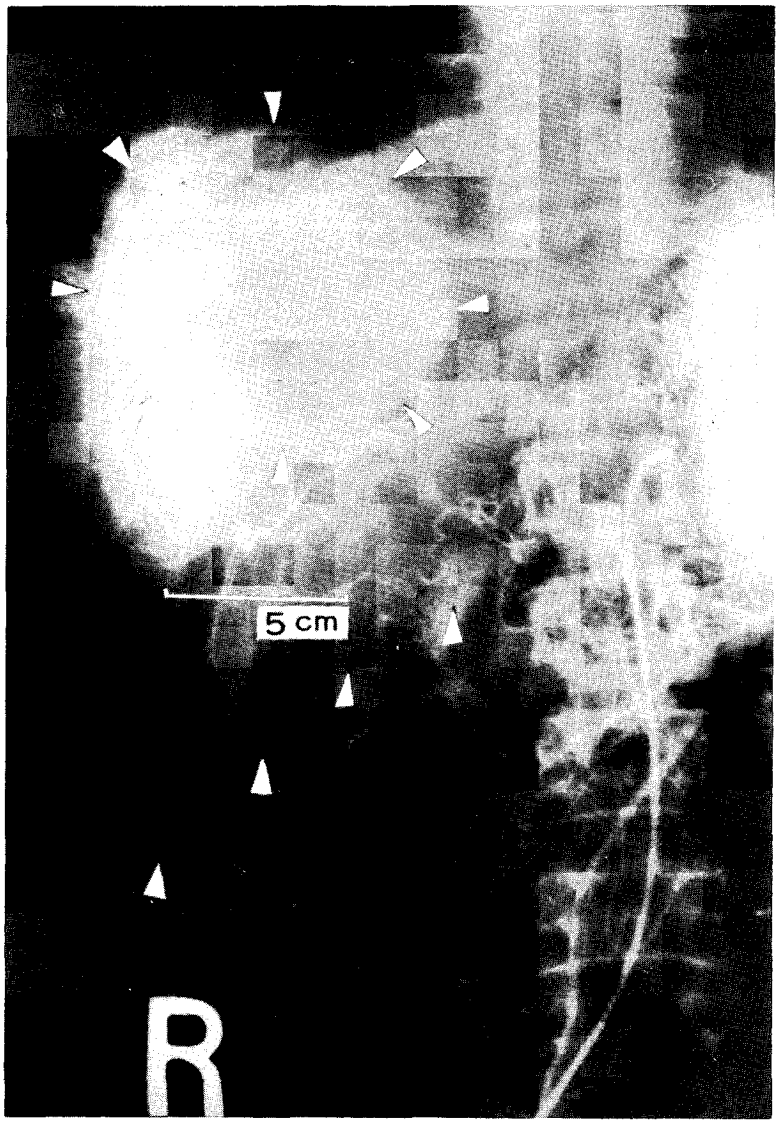

Fig. 6 Angiogram 1 month after total gastrectomy.

Then, streptozotocin was administered by intravenous drip infusion, in a dose of 500mg/m^2 /day, every day, over 5–6 days, every one to two months, starting at the end of May, 1974, with a total of 12 courses performed by October, 1975. Her general condition was so improved after the start of this therapy that she became able to sit up in daily life. The hypoglycemic manifestations disappeared about one month after the first course of treatment.

The hepatomegaly began to be reduced in size about two weeks after the first course , and from six months after the first course on, only the inferior margin of the liver was palpa-

ble one fingerbreadth over the right mammillary line in the deep part of the abdomen. The tumor shadows on the angiogram also regressed so markedly as to be each smaller than one half the size before the treatment (Fig. 6 and 7)

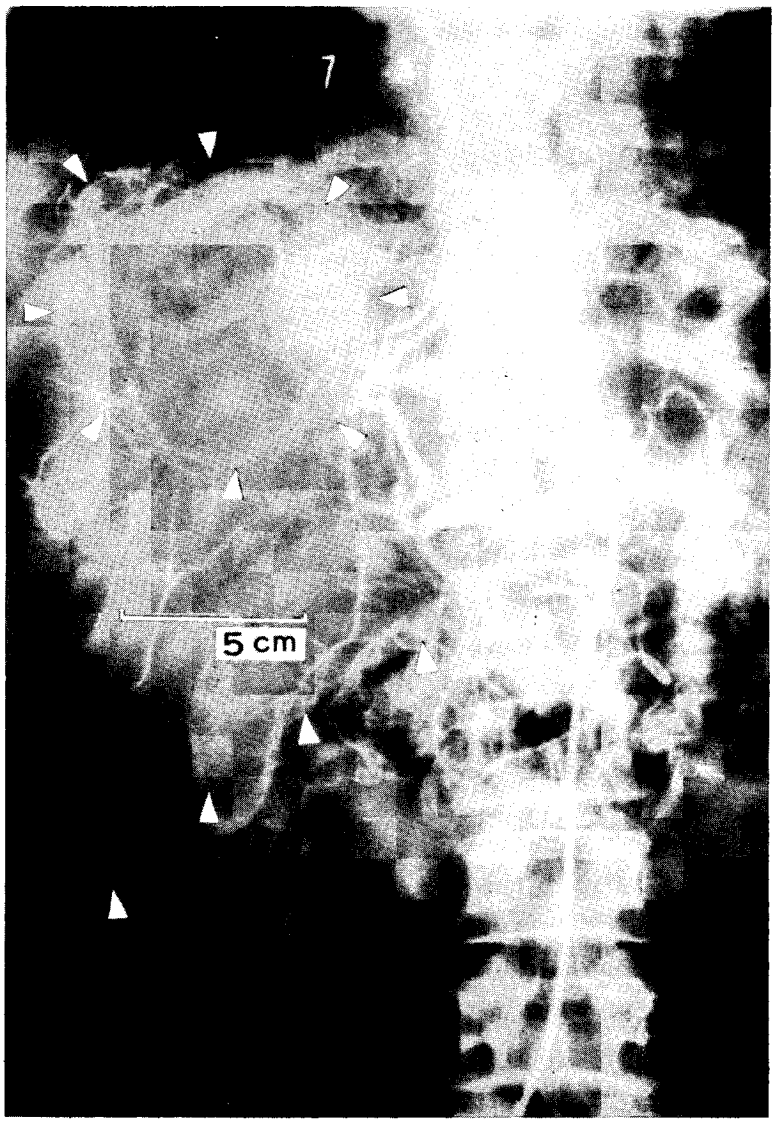

Fig. 7 Angiogram after the treatment with **streptozotocin,** Compared with Fig. 5, the liver and the metastatic focus in the liver, shown with arrows, have been greatly reduced in size.

Serum gastrin levels before the treatment were 580pg/ml in basal condition and 2850pg/ml after the injection of secretin 1U/kg. while, after the treatment they were 366pg/ml in basal condition and 862pg/ml even after the injection of secretin 3U/kg (Fig. 8). Glucose tolerance test, assessment of BUN and serum creatinine were repeated, and her glucose tolerance was revealed to be reduced.

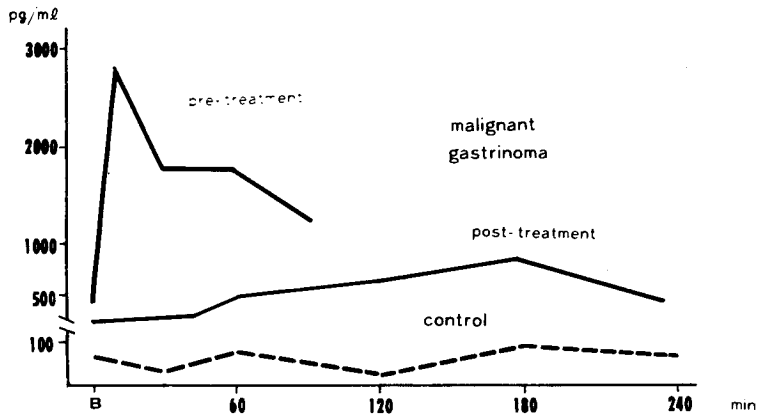

Fig. 8 Serum gastrin levels in basal condition and after secretin injection before and after the treatment.

Needle biopsy of the liver metastatic focus was done on July 29, 1976. The specimens were examined optic microscopically and electronmicroscopically.

Compared with surgical specimen before the treatment, the tumor showed, optic microscopically, marked degenerative changes revealing an enlargement or a condensation of cytoplasm and nucleus (Fig. 9)

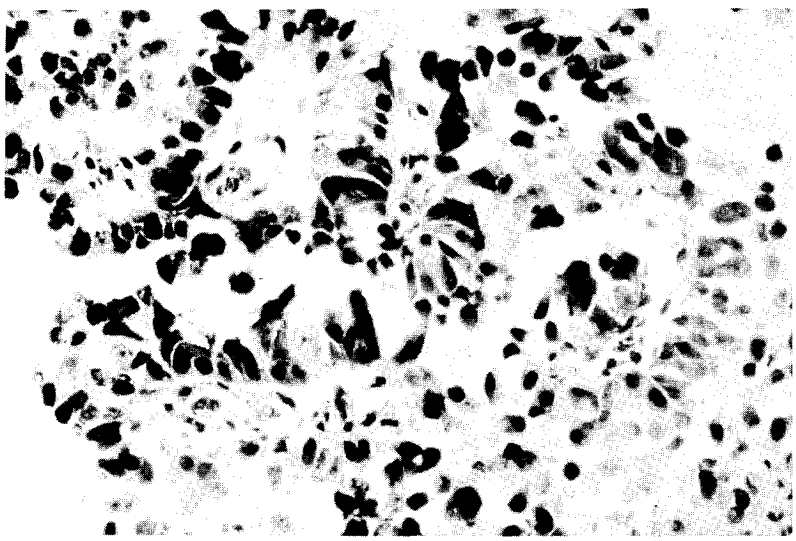

Fig. 9 Light microscopic picture from the liver metastatic focus obtained by needle biopsy after treatment with streptozotocin, showing irregular papillary arrangement of the tumor cells and cleft formation by detaching the tumor cells. The tumor cells show marked degenerative changes revealing enlargement or condensation of cytoplasm and nucleus. (H & E)

Electron microscopically, the tumor cells had many lysosomes in the cytoplasm and some revealed a cytosegresome or a collapse of the cytoplasm.

Those are the findings of degenerative changes of tumor cells too, suggesting streptozotocin has a good effect on this tumor (Fig. 10)

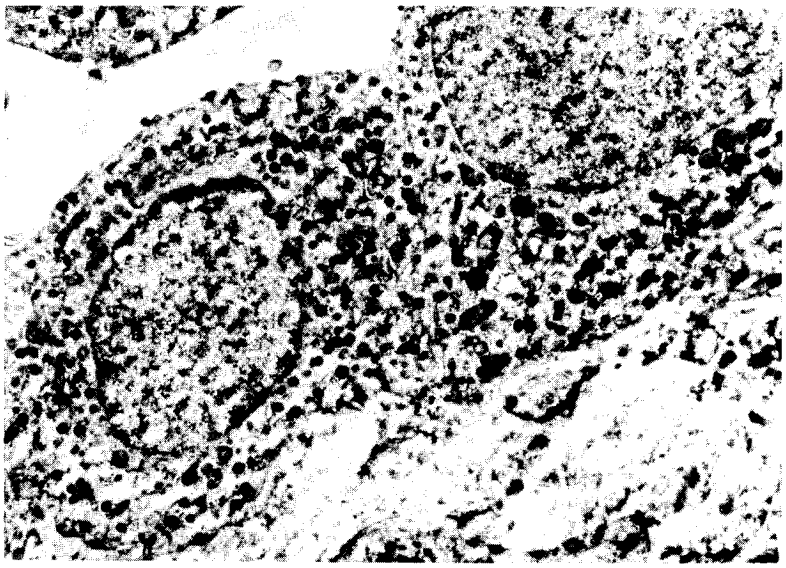

Fig. 10 Electron micrograph from the same specimen as Fig. 9. The tumor cells show relatively narrow and dense cytoplasm and ovoid or irregular shaped nucleus. The cytoplasm contains a lot of granule and well developed endoplasmic reticulum. The tumor cells have many lysosomes in their cytoplasm and some cells reveal cytosegresomes or collapse of their cytoplasm. The cytoplasmic granules are round in contour, 250–300nm in diameter, showing a variety of electron density without core.

From November, 1976 on, palpation of the abdomen disclosed a rapid enlargement of the liver, and angiogram exhibited a growth of the liver metastatic foci. From the end of July, 1977 on, ascites and dilatation of veins of the abdominal wall evolved, associated with intensified cachexia. From the middle part of August on, jaundice manifested, with the serum total bilirubin increased to 5.9mg/dl.

Starting on August 23, streptozotocin in a dose of 250mg/m^2/day was administered again by intravenous drip infusion daily for 5 days to about 1.7g in total. However, she died of cachexia and liver failure. At autopsy, metastatic and recurrent tumor was not found anywhere except for the liver.

However, almost all of the liver was replaced by metastatic tumors. Light microscopic examination of the liver did not reveal any remarkable degenerative changes of hepatocyte as well as tumor cell.

DISCUSSION

Almost all of the papers concerning Zollinger–Ellison syndrome (ZES) in Japan do not classify malignant gastrinoma. And only a few deal with the course, treatment and indices of observation of the course of this malignancy after total gastrectomy.

This phenomenon may be attributed to the generally accepted concept that ZES runs a favorable course after total gastrectomy.[7] Zollinger showed, however, that it is very pessimistic to eliminate large metastatic foci by total gastrectomy only.[3]

In the present paper, these factors are discussed with reference to the authors' case presented above in addition to the cases reported by other investigators.

1. Course and treatment of malignant gastrinoma after total gastrectomy

Zollinger reported the more than 19 years survival with disappearance of tumor of one of his first two total gastrectomy patients,[3] and Friesen also reported a similar experience.[2]

Wilson and Ellison disclosed that only four out of 78 total gastrectomy cases of ZES died of tumor and cachexia.[8] These descriptions seem to have given strong impressions to the investigators all over the world, especially to the Japanese workers, leading to such a thinking that prognosis is favorable in this disease after total gastrectomy.

The aforementioned finding by Wilson and Ellison, however, was not achieved in a study of malignant tumor; hence, it does not show the prognosis of this malignancy. It is said that out of 33 total gastrectomy cases of this malignancy registered in the Zollinger–Ellison tumor registry, 16 have died of progression of the tumor.[4] In Japan, we have collected 26 case reports and one personal communication of a case of malignant gastrinoma up to the present time[9]; out of 9 patients who had undergone total gastrectomy five died of the tumor and out of 18 patients who had not undergone total gastrectomy only three were alive and the other 14 died of the tumor. In our patient, the tumor continued to grow, being refractory to various anticancer agents, and she lapsed into cachexia in about one year.

Thus, malignant gastrinoma may vary considerably in the degree of malignancy from case to case, but this tumor may progress even after total gastrectomy. Therefore, a study on the treatment of this malignancy even after total gastrectomy is necessary.

At present, radiotherapy,[4] MMC therapy, 5-FU therapy, FAMT therapy and surgery against the liver metastases[4] seem to be ineffective in treating malignant gastrinoma, while streptozotocin has proved effective in five[4, 10, 11] and ineffective in one case[12] of this malignancy, including the case encountered by the authors where tumor regression was observed for 2.5 years, belonging to category 1–B of Karnofsky.

Stadil and his co-workers administered this agent in 2 cases intraarterially, and proved it to be effective. In our patient, light microscopic examination of the liver at autopsy did not reveal any degenerative changes of hepatocyte after intravenous streptozotocin therapy.

The authors, therefore, are of the opinion that streptozotocin is a drug worth trying in this malignancy and intraarterial administration of this agent may be done in low toxicity level.

2. Indices of observation of the course after total gastrectomy

In our patient, alterations in the general condition were so gentle that they could not be an index ; appetite and vigor were well maintained until the terminal stage, showing no explicit alterations.

Despite the presence of the giant metastatic foci in the liver, results of liver function tests remained normal until close to the terminal stage.

The assessment of the serum gastrin levels, on the other hand, proved useful.[13] In our patient, too, the serum gastrin increased. Attention has lately been called to the modes of alterations in the serum gastrine level with various loading tests such as bouillon, glycine,[14] calcium[15, 16] or secretin.[17] In our patient, the assessment of the serum gastrin levels with loading secretin seemed to be most useful.

There is a paper reporting that angiography is useful,[18] but it requires more studies on more patients to evaluate the significance of this method in following up malignant gastrinoma. In our patient, this technique proved useful for observing the hepatic metastases which were spheric and hypervascular. Thus, hepatic metastatic focus of this tumor was angiographically closer to insulinoma than to ductal adenocarcinoma of the pancreas.

Liver scan. also proved useful.[13] In our patient, intravenous injection of 4 mCi of ^{99m}Tc OH phytate gave filling defects corresponding to the site of tumor on the angiogram (Fig. 11).

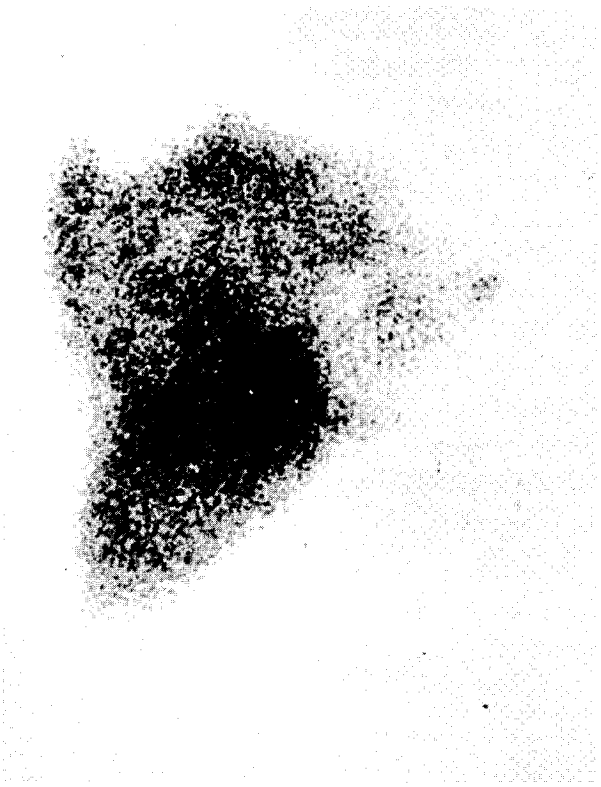

Fig. 11 Liver scan. on administration of 4 mCi of ^{99m}Tc OH phytate. The metastatic foci of malignant gastrinoma in the liver are seen as filling defects.

Passaro and his co-workers used liver scan., alterations in the serum gastrin level with intravenous injection of calcium and angiogram of the liver as indices.[4, 19] The authors consider that, additionally to them, assessment of the serum gastrin level on loading with secretin is also useful as one of indices of this malignancy.

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