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Hormone secreting tumors of the pancreas: Some insights into their clinical and fundamental interest

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Clinical and fundamental research have been progressing simultaneously in the field of hormone secreting tumors. Concerning fundamental research the interest of human endocrine tumors was originally recognized for pituitary and adrenals. For non-steroid hormones, the importance of clinical studies was later on disclosed with improvement of diagnosis of insulinoma and serotonin-secreting tumors. As far as pancreatic tumors are concerned, gastrinomas with the Zollinger-Ellison syndrome (ZES) as clinical presentation were as early as 1968 exceptional material for basic research in molecular forms of gastrin and in gastric secretion mechanism.

Gastrinoma or Zollinger-Ellison syndrome (ZES): an elective model (1)

Clinically ZES (1) is expressed in 85% of cases as a very common disease, peptic ulcer. 1/1000 is the approximative prevalence of ZES in patients with duodenal ulcer. Diagnosis of ZES is now more easily obtained with better clinical recognition, the use of provocative tests (secretin test) and progresses in imagery (CT scan, arteriography). Besides therapy with specific drugs, mostly gastric antisecretory substances (H2-blockers; benzimidazole derivatives) (2), attempts to excise the tumoral process is a major therapeutic orientation.

Hepatic metastases (HM) are often the only evidence of malignancy in the ZES. In a personal series (3) of 144 consecutive ZES cases with a mean follow-up period of 50 months, prevalence of HM was 25%. Preoperative imagery gave the final diagnosis of HM in only half of the cases. In the other half of the cases, diagnosis was obtained by systematic laparotomy.

HM were responsible for 50% of the 46 non-operative deaths. At 5 years, 5 of 29 patients (17%) of the synchronous HM group were still alive vs 65% for the entire population.

Results of chemotherapy for HM in Zollinger-Ellison syndrome was recently analyzed in the largest published series resulting from a multicentric study (4). 45 ZES patients were treated by Streptozotocin (STZ) for HM in 12 European, American or Australian centers.

In the majority of the cases, treatment modalities were those proposed by Moertel (5). Actually, total STZ dosage was highly variable (median value : 10 g/sqm, extremes : 2.5—87). Route of administration was intravenous, into the hepatic artery or both. 5 FU was associated in 28 patients, dauxorubicin in 9 and tubercidin in 4.

Therapeutic effect was appreciated according to OMS criteria, HM size being measured by the best imaging technique for each patient (ultrasonography, CT scan, arteriography). Objective response was noted in 42% of the cases : 9 complete remissions, 10 regressions with a latence of 17 weeks in mean. Stability was noted and tumor progression in 13.

Toxicity was limited to nausea and/or vomiting (84%) and to transient mild proteinuria or tubulopathy (30%).

In conclusion, except insulinoma, ZES is the most frequent presentation of pancreatic tumors with hormone secretion. Thus diagnosis is often discussed in the presence of ulcer disease and/or steatorrhea. Diagnosis is better suggested by routine gastric secretion studies than gastrin measurement, but a provocation test with secretin infusion and simultaneous measurement of serum gastrin and gastric acidity is the best tool for obtaining diagnosis certainty. Prognosis has been largely improved by the development of 1) gastric antisecretory drugs for suppressing the harmful situation due to gastric hypersecretion, 2) Chemotherapy of liver metastases, 3) More ambitious tumor surgery in well-defined conditions.

As far as basic research is concerned gastrinomas are a source of precious material. In this tissue gastrin secretion is very intense and obviously represents the major (if not unique) activity of the tumor. Thus, biological studies can be carried out either on dispersed tumoral cells from fragment surgically collected from pancreatic and metastatic gastrinoma or from cultures.

Initial by work Lichtenberger et al (6) did not succeed in obtaining either a survival time of the primary culture over 6 weeks or an adequate responsiveness to hormonal stimulants.

According to Ellison et al. (7), acute gastrinoma cell dispersion experiments allow to measure gastrin concentration in the medium and the pellet in the basal state and after stimulation but with a rapid fading in the release.

In our group (8), starting from tissues of 5 patients (4 pancreas and one liver metastasis) successful cultures were obtained with internative passages and a survival time of gastrin secreting endocrine cells presently over 5 months. Responsiveness of the model to stimulants (DB cAMP, Ca^{++}, bombesin, carbachol, secretin, phorbol ester) and to inhibitors (somatostatin) was successfully tested with excellent reproducibility and no time-related fading. Immunochemical (immunogold) evidence was obtained in many cases for the structural identities of the cultured cells with the initial sampling concerning morphology and hormone secretion. Some features of the cell structure exhibit modification, however particularly in granule density and shape.

Multiple-hormone secreting tumors and MEN I (9,10)

Ectopic hormone production is the phenomenon by which certain neoplasms produce hormones not usually produced in significant amount by tissues from which neoplasms arise. Pancreatic gastrinoma gives rise to ectopic hormone production since gastrin is not normally secreted by the endocrine pancreatic tissue. In this condition multiple hormone production (10) is not uncommon: the most frequently observed are VIP (5—10%), glucagon (10—20%), somatostatin (10—20%), PP (15—20%), insulin (20—30%), ACTH (10—30%). For fundamental research, ectopic hormone-producing tumors provide a potential model for investigating the control of gene expression, especially the differences between ectopic hormone and entopic hormone production.

MEN I fundamentally raises the same kind of problems (9). Prevalence in ZES is over 25%. Parathyroid involvement is the most frequent (82% of ZES with MEN I). The high rate of relapse after parathyroidectomy (in contrast to primary adenoma) implies the presence of a systemic stimulatory factor in keeping with the diffuse pancreatic lesions constantly observed in ZES with MEN I (at variance with sporadic ZES).

Vipoma or Verner-Morrisson Syndrome: cAMP activation and relevant symptoms (11, 12, 13).

They are rare tumors and the published cases of the largest series involve no more than 200 patients. Neuroendocrine tumors that elaborate vasoactive intestinal polypeptide (VIP) in excess are found in the pancreas (90%) and in neural tissue (neuroblastomas, ganglioblastomas) of the autonomic nervous system (10%) including the adrenal medulla. Single primary neoplasms constitute 80% of the pancreatic tumors, but hepatic metastases do occur in about one-half of them; islet cell hyperplasia is present in 10 to 20% of the patients. There is good evidence that the cellular source of VIP may be the neural cells within the pancreas and/or the endocrine cells of the islets (12). Thus there is a dual role for VIP, neural modulation and endocrine. The potent endocrine function of vipomas stimulates cyclic AMP in the exocrine cells of the gut to produce a massive secretion of water and electrolytes into the small intestine that overwhelmes the normal absorptive capacity of the colon. Because VIP is a molecular member of the secretin-glucagon family, it has endocrine functions similar to secretin, such as increased pancreatic bicarbonate excretion and gastric acid inhibition, as well as a glucagon-like action of abnormal glucose tolerance. There is also a vasomotor action of VIP that causes vasodilatation.

Thus, the most prominent feature clinically (11,13) is the profuse watery diarrhea in volumes often exceeding three liters per day; it may be explosive, episodic and may occur even during fasting. The resulting dehydration and hypokalemia produce weakness that may progress to hypotension, compounded also by the accompanying vasodilatation. Either hypochlorhydria or achlorhydria is frequently observed in spite of normal parietal cells being present in the stomach. Distended and enlarged gallbladders have been observed. The lethargy seen in approximately 50% of these patients may be due in part to the hypercalcemia. Increased plasma concentration of VIP is a major argument for diagnosis.

Vipoma is a model for intestinal absorption and secretion studies (14); an increase in adenylate cyclase activity of the enterocytes may be main explanation for diarrhea, although other diarrheogenic hormones (PP, PG, calcitonin) might be also secreted by the tumor. This biological responsiveness of enterocytes to VIP was proposed as a basis for a biossay (13). Paradoxical observation of cAMP stimulation of the gastric musoca with acid secretion inhibition is not yet fully understood.

Somatostatinoma: a suggestive model for the therapeutic use of somatostain

The syndrome produced by excessive elaboration of somatostatin has been designated the inhibitory syndrome because of its physiologic and pharmacologic effects of inhibition of the release of insulin, glucagon, gastrin, and cholecystokinin (16). Its inhibitory actions on secretin, vasoactive intestinal polypeptide, motilin, thyroid-stimulating hormone and growth hormone are not clinically apparent in the syndrome. The clinical findings associated with the presence of a somatostatinoma include diabetes, cholecytolithiasis, steatorrhea, indigestion, hypochlorhydria and,

occasionally, anemia (11,17). Less than 30 patients have been reported to have somatostatinomas.

Here again, pathophysiological studies could be based on cell biology concepts (18). Somatostatin receptors are diffused in the body and receptor studies, even on isolated cells, could lead to a better understanding of the biochemical background (19,20). However adaptation to a greatly excessive release of somatostatin is apparently good for a long period of time without endangering life.

The use of somatostatin in the management of hormone-secreting tumors, particularly those located in the digestive tract, was proposed more than 10 years ago. The inhibitory effects of somatostatin on the secretion of most gut hormones brought high hopes of a beneficial effect of chronic therapy with this type of patients. Only recently has the new molecular form, SMS 201-995 (Sandostatin), allowed the overcoming of problems in the short duration of action natural somatostatins and particularly the requirement of administration by infusion (21, 22, 23).

In ZES, numerous publications evidenced ability of SMS to decrease serum gastrin and acid secretion for several hours after a single subcutaneous injection; only recently its practical usefulness in a management scheme, applied over months or years, has been tested by our group. Five patients were to treated during 9 to 12 months. Basal acid output presented a sustained decrease in 4 out of 5 cases, allowing ranitidine discontinuation. The serum gastrin level was affected to a greater extent showing a mean 87% decrease throughout the treatment period. Tolerance of SMS was excellent and we concluded that antitrophic and antigastrin properties of SMS could improve the therapeutic efficacy in long-term management of ZES (22).

In VIPoma patients the beneficial action of SMS was readily shown. The diminution in the elevated circulation of VIP was probably not enough to explain the outstanding clinical improvement. A direct inhibitory effect on the gut (transit time, electrolyte absorption, jejunal secretion) has to be hypothesized (24).

Exciting aspects of these therapeutic effects of SMS 201-995 were the shrinkage of the primary tumor or hepatic metastases in a minority of patients (25, 26). It is too early to conclude whether this anti-tumor effect of the analogue will contribute to a prolongation of the survival of these patients.

The future of SMS use would probably become clear after receptor studies (27) giving prevision on the usefulness and the efficacy of this promising hormonal therapy.

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