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Zollinger-Ellison Syndrome In Men1 Patients: Medical Or Surgical Treatment?

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Editorial

Multiple endocrine neoplasia type 1 (MEN1) is characterized by the occurrence of tumors in different endocrine organs mainly parathyroid glands, pancreatic islets and anterior pituitary glands. The pancreato-duodenal neuroendocrine tumors (NET) have a high penetrance with a prevalence of 9%, 53% and 84% at 20, 50 and 80 years of age, respectively [1]. Pancreato-duodenal NETs may secrete hormones that provoke a clinical syndrome of hormonal excess or not secrete hormones (non-functioning NETs). Gastrinomas are the most frequent functioning pancreato-duodenal NET which can cause gastric acid hypersecretion with the manifestation of the Zollinger-Ellison syndrome (ZES). The hypergastrinemia has a throphic effect both on gastric mucosa and on gastric enterochromaffin cells (ECL). It is diagnosed in at least 50% of MEN1 patients at an age of 50 years ca, with prevalence in men [2,3]. At the moment of the diagnosis, pancreatic non-functioning NETs are usually detectable in all patients [2]. The great majority of the MEN1-gastrinomas (>90%) are found in the deep layer of the duodenal mucosa within the Brunner's glands or in the duodenal submucosa. This aspect is in contrast to the sporadic gastrinoma that is found prevalently in the pancreas [4]. MEN1 associated duodenal gastrinomas are usually multiple, less than 5 mm in diameter, and well differentiated with a low K1 67 (less than 2%) [5]. The metastatic potential of most duodenal gastrinomas is restricted to the peripancreatic lymph nodes which are positive in 34% to 85%. These lymph node metastases do not adversely affect survival [2,5-8] There is general agreement that duodenal gastrinomas have exceptionally fast growth or metastatisation to the liver.

On the other hand, pancreatic gastrinomas are very rare in MEN1 patients. Donow et al. [9] found a pancreatic gastrinoma in only one of 18 (6%) patients with ZES and MEN1. Imamura et al. [10] found a pancreatic gastrinoma in 2 of 18 (11%) MEN1 patients who had been submitted to surgery for ZES. In the personal experience regarding 20 patients with ZES and/or hypergastrinism and positive secretin test, a pancreatic gastrinoma was found in only one patient [11]. In our patient as in those studied by Imamura, the pancreatic gastrinomas were concomitant to duodenal gastrinomas. Other authors found a higher incidence of pancreatic gastrinomas in MEN1 patients: 42% according to Gibril et al. [12] and 18% according to Lopez et al. [5]. This could be due to the different histopathological criterion followed for diagnosis. In a third of the cases, the pancreatic gastrinoma is associated to aggressive behavior (fast growth, local invasion, and/or liver metastasis). Factors predictive of the aggressive form are: age at MEN1 diagnosis <35 years, age at ZES onset <27 years, fasting gastrin levels >10.000 pg/ml, dimension >3 cm [12].

Ectopic gastrinomas can be rarely present in MEN1 associated: 5 cases were found in the extrahepatic biliary tree and 1 in the liver.

Interestingly, ectopic gastrinomas can be the cause of persistence or recurrence of the ZES after resection of duodenal gastrinomas [13-15].

The natural history of MEN1 associated gastrinomas is not completely clear since few studies have prospectively collected data submitting the patients to a scheduled protocols of exams and adoption of rigorous criteria of treatment. Considering the NIH experience (one of the largest in the world) that prospectively followed 106 patients and submitted them to periodic controls and appropriate therapeutic interventions, the overall survival at 5, 10, 20 and 30 years post diagnosis of MEN1 gastrinomas is 95.3%, 89%, 67.5% and 55% respectively [2]. Twenty-three of the MEN1 patients had died at a follow-up of 15.5 years (as a mean). The mean age of death is 55 years (less than that expected for the general population). However, the most common (58% of cases) cause of the death is related to metastatic spread of malignant pancreatic NETs or thymic carcinoid tumors rather than gastrinomas. Therefore, is not clearly established in the NIH study whether the duodenal gastrinomas are responsible for death.

The treatment of MEN1 associated gastrinomas can be addressed to the control of the gastric hypersecretion only, or to the surgical excision of the gastrinoma(s). In the past, to eliminate the dramatic consequences of gastric hypersecretion (life-threatening gastrointestinal hemorrhage or perforation) total gastrectomy was the treatment of choice. The natural history of gastrinomas is dramatically changed following the advent of histamine-2 receptor antagonists (i.e., cimetidine, ranitidine, famotidine), proton pump inhibitors (PPIs: i.e., omeprazole, lansoprazole, pantoprazole) and somatostatin analogues (i.e., octreotide and lanrotide). These drugs, whether employed singularly or in association, have shown control and resolution of ZES complications, long-term effectiveness, and absence of important side effects. PPIs can be used for long periods of time without loss of effect, since tachyphylaxis does not occur [16]. Somatostatin analogs have also demonstrated to control the growth of gastro-entero-pancreatic NETs, but no data are available regarding their effects on the growth of MEN1 associated gastrinomas [17].

Reasons to operate on gastrinoma(s) are the following: 1) to avoid neoplastic progression; 2) to restore normal gastrinemia and prevent the formation of gastric carcinoids. However, the choice between prolonging medical therapy or moving to surgery usually depends not only on the presence of gastrinoma(s), their growth and/or the increased values of gastrin, but overall on the appearance or growth of concomitant NETs in the pancreas. The guidelines of the scientific societies and the consensus of the experts agree that pancreatic nodules that significantly grow (doubling their size over a 6 month interval), or approach the 2 cm in diameter, present a mandatory indication for surgery, in order to avoid the development of a neuroendocrine carcinoma and prevent local invasion and/or liver metastases [18-21]. Indeed, a relationship between the size of

pancreatic NETs and the presence of liver metastases has been found (10% if NETs are 1.1-2.0 cm; 18% if 2.1-3.0 cm and 43% if >3.0 cm) [22]. When the decision to operate is posed, the treatment should be addressed more to the excision of the pancreatic NETs than the concomitant gastrinoma(s). Most of the time, several NETs are scattered in the pancreas. All pancreatic NETs greater than 1 cm should be excised in order to avoid reoperation or risk of carcinoma. Total pancreatectomy must be exceptionally employed for avoiding the consequences of endocrine and esocrine pancreatic insufficiency. Resection of the most affected part of the pancreas and enucleation of one or two residual NETs in the preserved pancreas should be the treatment of choice. Pancreatic enucleation should be employed with caution considering the risk of damage to the Wirsung duct, inadequacy for malignant NETs, and difficulty in the presence of multiple or deep macroadenomas.

When pancreatic NETs are prevalently located in the right pancreas, pancreato-duodenectomy (Whipple operation) or pylorus preserving pancreato-duodenectomy should be preferred with a high probability (around 80%) of being curative for hypergastrinism since all the duodenum where most of the gastrinomas are present and can recur, is removed. Vice versa, when pancreatic NETS are predominant in the left pancreas the Thompson's procedure is chosen. This type of surgery consists in performing a longitudinal duodenotomy with mucosal enucleation or full-thickness duodenal wall excision (if the gastrinoma is >0.5 cm) of the discovered duodenal gastrinomas and a peripancreatic lymph-node resection associated to the corporo-caudal pancreatic resection and/or enucleation of tumors in the pancreatic head if pancreatic NETs were present [8]. This type of surgery avoids total pancreatectomy and ameliorates the hypergastrinism, even if the biochemical cure of the gastrinomas is rarely achieved. Pancreas preserving total duodenectomy is another option for patients in whom macroadenomas of the pancreatic head are absent [10]. It consists in the resection of the entire duodenum and gastric antrum, the ligation of the accessory pancreatic duct, the sphincterotomy of the major papilla after removing its mucosal lining, and the anastomosis of the Vater papilla on a Roux-en-Y jejunal loop. In the experience of Imamura et al [10], pancreatic resection of the distal pancreas was needed in 5 of the 7 operated patients, and biochemical cure of the hypergastrinism was achieved in 5 of the 7 patients. Looking at surgical experience of the last 20 years, the mortality of pancreatic resections is almost always absent and the number of complications is not particularly high and frequently resolved without reintervention. However, pancreatic resections are at risk for the occurrence of diabetes mellitus, and this complication can be a main cause of a compromised quality of life. Currently, the benefits of these surgical options have not been tested against medical treatment with PPIs and/or somatostatin analogues.

Do we really have to worry about gastric carcinoids? Hypergastrinemia promotes the occurrence of gastric carcinoids (the so called type II) in MEN1 patients. These tumors have a median size of just a few millimeters, are multiple, grow in the mucosa or submucosa, and are always associated to hyperplasia of the ECL cells (36). It seems that many years are necessary for the development of these tumors, and that they remain stable for a long time. Indeed, they generally have benign behavior metastasizing rarely (in the order of 10%), and prevalently to local lymph nodes rather than to the liver (38). The normalization of the serum gastrin levels after gastrinoma resection in MEN1 patients allows the regression of the ECL cells hyperplasia and of the gastric carcinoids (at least of those smaller than 1 cm in diameter) [23]. Therefore, the rational treatment should be to remove all gastrinomas. However, considering the good prognosis of the type II gastric carcinoids, a conservative approach by endoscopic surveillance and excision of the tumors when their dimension increases is justified. More experience will be necessary to confirm if this approach is right [24]. Somatostatin analogues have also been employed for the treatment of type II gastric carcinoids with a significant reduction in gastrin levels and tumoral dimension [25].

In conclusion, the great majority of gastrinomas in MEN1 patients are located in the duodenum; they are characterized by indolent growth and a good prognosis, even if they frequently metastasize to the regional lymph nodes. ZES is present in more than 50% of the cases, but is well controlled by PPI administration. The timing of surgery is determined by the presence and growth of non-functioning pancreatic NETs. Surgery should first directed at removing pancreatic NETs and second to treating gastrinomas. The most affected part of the pancreas must be resected and the enucleation should be reserved for any macroadenomas in the pancreas that is preserved. Doing this also removes any pancreatic gastrinoma that may become aggressive. Surgical resection of the gastrinomas is curative in a high proportion of cases. The risk of the occurrence of a gastric neuroendocrine carcinoma can be also prevented by this policy.

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