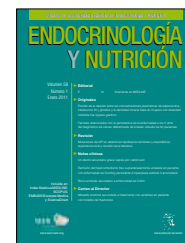




ENDOCRINOLOGÍA Y NUTRICIÓN

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REVIEW

About a case of multiple endocrine neoplasia type 1. Review of some clinical manifestations and treatment controversies

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Abstract Multiple endocrine neoplasia type 1 (MEN1) is a rare hereditary syndrome known to predispose subjects to endocrine neoplasms in a variety of tissues such as the parathyroid glands, the pituitary gland, and the gastrointestinal tract. We report the case of a male patient who, in addition to the traditionally described conditions (hyperparathyroidism and gastrinoma), was found to have other tumor lesions arising from both endocrine cells (insulinoma, gastric carcinoid, adrenal adenoma, and non-functional pancreatic neuroendocrine tumors), and non-endocrine cells (lipoma and collagenoma). The frequent recurrence of lesions in not completely resected susceptible tissues (as occurs in hyperparathyroidism and duodenal gastrinoma) as well as doubts concerning their clinical significance in MEN1 has raised some questions regarding the therapeutic management of such lesions, and this controversy is briefly reviewed.

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PALABRAS CLAVE

Insulinoma;
Gastrinoma;
Hiperparatiroidismo;
Tumores
neuroendocrinos;
Neoplasia endocrina
múltiple

A propósito de un caso de neoplasia endocrina múltiple tipo 1. Revisión de algunas manifestaciones clínicas y controversias en el tratamiento

Resumen La neoplasia endocrina múltiple de tipo 1 (MEN1) es un síndrome hereditario raro conocido por la predisposición a la aparición de neoplasias endocrinas en distintos tejidos como paratiroides, hipófisis y tracto gastrointestinal. Se presenta el caso de un varón en el que además de manifestaciones tradicionalmente descritas (hiperparatiroidismo y gastrinoma) se objetivaron otras lesiones tumorales procedentes de células de estirpe endocrinológica (insulinoma, carcinóide gástrico, adenoma suprarrenal, tumores neuroendocrinos no funcionantes del páncreas) y no endocrinológica (lipoma y colagenoma). La frecuente recurrencia de las lesiones

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sobre los tejidos susceptibles no resecaados en su totalidad (como en el caso del hiperparatiroidismo y del gastrinoma duodenal) y las dudas sobre su significado clínico en el MEN1 suscitan cierta controversia en la actualidad sobre las recomendaciones en el manejo terapéutico de dichas lesiones que se revisa brevemente.

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Introduction

The reported case allows for the review of two current issues related to multiple endocrine neoplasia type 1 (MEN1): the diversity of potentially associated tumors other than those traditionally reported¹ and the continuing controversy concerning their treatment, particularly for neuroendocrine tumors (NETs) in the gastrointestinal tract, such as gastrinoma².

Case report and course

A 28-year-old male patient was admitted in March 1985 for an etiological study of a tonic-clonic seizure concomitant with a capillary blood glucose value of 25 m/dL which subsided upon intravenous administration of glucose. The patient had a medical history which included recurrent renal colic over the previous year. Moreover, his father had died at 45 years from a malignant neck tumor, and had had a prior history of complicated peptic ulcer requiring gastrectomy. Laboratory tests showed a corrected calcium value of 11.9 mg/dL (normal range [NR], 8.5-10.5) attributed to primary hyperparathyroidism (PHP) and a serum PTH level of 549 pg/mL (NR: 10-65). Twenty-four hours after a fasting test, the patient experienced disorientation and drowsiness with a venous blood glucose value of 27 mg/dL and an insulin level of 22 μ i/mL with no sulfonylurea intake. The association of endogenous hyperinsulinism and PHP suggested the presence of MEN-1 syndrome. Tests to detect insulinoma included an abdominal ultrasound which revealed a 2-cm nodule in the body of the pancreas, which was confirmed in an arteriography which showed another nodular 0.5-cm lesion in the tail of the pancreas. During surgery, additional nodules were found in the body and tail of the pancreas, and a corporocaudal pancreatectomy was therefore performed, in addition to peripancreatic lymphadenectomy and splenectomy. A pathological study documented the presence of 13 NETs (two of them 2.2 cm and 2 cm in size, and all other tumors smaller than 1 cm), with infiltration of one of the lymph nodes. Although confirmatory immunohistochemistry was not available, the clinical course, with the disappearance of hypoglycemia and the appearance and persistence of abnormal fasting glucose, led to diagnosis of a multicentric insulinoma resolved after surgery.

Screening for other primary neoplasms associated with MEN1 at that time proved negative: fasting gastrin 65 pg/mL (NR: 25-115), postoperative abdominal CT with no evidence of other tumors, normal basal hormone study and pituitary MRI.

Surgery for PHP, performed two years later, consisted of subtotal parathyroidectomy sparing part of the right upper parathyroid gland. Calcium levels remained normal until

June 1997, when the asymptomatic recurrence of PHP (calcium 10.5 mg/dL and iPTH 103 pg/mL) was observed on the remaining unresected gland. A genetic study found a mutation in exon 9 of locus 11q13 codon 423 (cytosine to thymine). The patient remained asymptomatic until March 1998 (13 years after laparotomy), when abdominal pain led to endoscopic diagnosis of an ulcer in the first duodenal portion, which was treated with omeprazole. Despite a satisfactory response to proton pump inhibitors, abdominal pain recurred, accompanied by diarrhoea, whenever treatment was discontinued. The proton pump inhibitor was therefore continued. Gastrin levels had remained within the normal range up to a year before the ulcer episode (reaching 128 pg/mL in the absence of proton pump inhibitors). Gastrin levels were sequentially measured under omeprazole treatment at a constant dose of 20 mg/day and showed a gradual increase, as seen in Table 1.

Imaging tests (ultrasound, CT, MRI) looking for a possible gastrinoma were negative between 1998 and 2006, and positive images coincided with a marked gastrin elevation at that time. However, examination and imaging tests performed on the patient during this time revealed other lesions:

- A 1-cm gastric carcinoid, was found and resected during a high gastrointestinal endoscopy in 2002 (the endoscopy was performed to look for a duodenal gastrinoma and rule out chronic atrophic gastritis as a cause of hypergastrinemia -with negative results in both cases).
- Papular lesions in the left forearm consistent with collagenoma were found on physical examination.
- Enlargement of the right upper parathyroid gland since 1997.
- Lesions consistent with subscapular and pleural lipomas since 2006.
- A nodule suggesting a right adrenal adenoma since 1998 (1.5 cm in size initially and 2 cm in size in 2009) with negative functional study.

From January 2007, after biochemical confirmation of gastrinoma by a secretin test, abdominal CT and MRI showed a new hypervascularized lesion meeting radiographic criteria

Table 1 Change in serum gastrin levels between 1999 and 2008

	1999	2000	2001	2007			2008
				March	August	October	
Gastrin	163	165	191	583	1,000	1,021	3,864

of NET, adjacent to the head of the pancreas, whose cross-sectional diameter increased from 1 cm in January 2007 to 2 cm in February 2008 and to 3 cm in May 2008 and which showed positive uptake on an octreoscan. An echoendoscopy with biopsy performed in July 2008 confirmed the presence of a 3-cm lesion adjacent to but separate from the head of the pancreas with immunohistochemistry positive for chromogranin A and gastrin. The lesion site could not be established. Obvious lesion enlargement led to a new laparotomy being performed in April 2009 and consisting of:

- Resection of a 5 x 3.5 x 1.3 cm lobulated lesion adjacent to the head which was found to be a nodal metastasis of a well-differentiated NET with Ki-67 index lower than 5% and strongly positive for gastrin at immunohistochemistry.
- Enucleation of two intrapancreatic nodules found on manual examination of the head, consistent with non-functional NETs of 0.8 and 0.3 cm (negative for gastrin and insulin at immunohistochemistry).
- Cholecystectomy. A duodenotomy was not performed.

Two months later, normal gastrin levels were found (103 pg/mL) and the proton pump inhibitor was discontinued, but a pathological increase occurred after secretin infusion (peak of 675 pg/mL), and no peripancreatic lesion was found in a control CT scan. A diagnosis of resection of nodal metastasis from a gastrinoma with persistence of primary tumor was thus established. At the time of writing, the patient is in good general health, leads an active life, and has no symptoms despite the recurrence of PHP and the biochemical persistence of gastrinoma. He is being treated with omeprazole (20 mg/day) and has been receiving somatostatin analogues (octreotide LAR 20 mg IM every 4 weeks) for the past few months in order to prevent the malignant progression of primary gastrinoma.

Discussion and review

While the presence of two of the three main neoplasms (PHP, enteropancreatic NET, and pituitary adenoma) is sufficient to establish the existence of MEN1, the predisposition to other neoplasms in both endocrine and non-endocrine tissues is obvious¹. The endocrine tumors most prevalent in the general population include carcinoids (thymic carcinoids in 5% of MEN1³, and bronchial and gastric carcinoids in 2% and 10% respectively¹). Gastric carcinoids are usually found incidentally, as occurred with this patient⁴. Their small size allows for complete endoscopic resection of the non-functional tumor in most cases⁵. While sustained hypergastrinemia is a known stimulus for the proliferation of enterochromaffin-like cells, patients with sporadic Zollinger-Ellison syndrome have a slight risk of gastric carcinoid. Patients with Zollinger-Ellison syndrome associated to MEN1 have a 20 to 30-fold greater risk⁶, and gastric carcinoid should therefore be included in the spectrum of endocrine tumors associated with that condition, as is confirmed by the demonstration of inactivation of both copies of the MEN1A tumor suppressor gene in cells from gastric carcinoids of MEN1 patients⁷.

Other neoplasms found in this patient and already reported in MEN1, but of little prognostic impact, included an adrenal adenoma, found in approximately 30% of cases in some series⁸, skin and visceral lipomas found in 40%¹, and collagenomas found in up to 70% of cases⁹.

As regards PHP, it is the most common manifestation, with a penetrance close to 100% at age 50¹⁰. Our patient was diagnosed at an early age, which agrees with the medical literature. The involvement of multiple parathyroid glands, not always occurring at the same time, represents another difference from sporadic PHP and explains the high 67% recurrence rate in unresected residual parathyroid tissue (as occurred in the reported case) at 8 years of subtotal parathyroidectomy¹¹. This high recurrence rate could be the result of the inexorable evolution of genetically susceptible parathyroid glands¹². A different surgical approach is therefore recommended for PHP in MEN1 as compared to sporadic PHP. Surgery should consist of subtotal parathyroidectomy¹³ or even total parathyroidectomy with reimplantation of a gland in the forearm¹⁴. The high rate of permanent hypoparathyroidism after total parathyroidectomy and the high recurrence rate after subtotal parathyroidectomy have resulted in different opinions as to the best surgical approach.

Insulinomas in MEN1 are often described as small and multicentric tumors along the pancreas (as suggested by the histological study of the patient). For most authors, this makes corporocaudal pancreatectomy with examination of the head (enucleating any lesions) the surgical procedure of choice¹⁵. This would prevent the recurrent hypoglycemia reported in 40% of MEN1 undergoing multiple enucleations¹⁶ (usually sufficient in sporadic insulinoma), which mimics the genetic nature of the disease at the pancreatic level too¹⁷. For insulinoma, surgery is clearly indicated because of its usually curative outcome and the poor efficacy of the available medical treatments.

Among functional enteropancreatic NETs, gastrinoma is the most common neoplasm in MEN1, found in 60% of cases¹⁸. Unlike in the sporadic form, indication of surgery is controversial² despite the fact that gastrinoma is the main prognostic determinant because of its potential malignancy (liver or nodal metastases occur in almost half of all patients¹⁹). Unlike in insulinoma, the clinical manifestations derived from acid hypersecretion induced by gastrinoma (peptic ulcer, heartburn, diarrhoea) are successfully controlled in the long term with antacids such as proton pump inhibitors²⁰, whose efficacy has made previous gastric surgery procedures for the control of acid secretion redundant¹⁷. Thus, the main current objective of surgery for gastrinoma is to prevent or delay the occurrence of liver metastases in order to prolong patient survival²¹. Indeed, liver metastases, occurring in 24% of gastrinomas²², represent the main predictor of mortality in both sporadic and MEN1 forms. Survival rates are 93% at 15 years of follow-up and 26% at 10 years of follow up, respectively, in patients with or without metastasis at diagnosis²³. In sporadic forms, while resection often does not achieve a long-term cure (only 34% of operated patients have normal basal and post-secretin gastrin levels at 10 years²⁴), it is related to a lower rate of liver metastases (23% versus 3% at 8 years in non-surgical versus surgical patients²⁵) and specific mortality (23% versus 1% at 12 years respectively²⁶). In MEN1, the

controversy concerning the suitability of the surgical approach for gastrinoma is due to several factors:

- The poorly known natural history of the tumor, with long-term survival reported in some series (88% to 100% at 10 years) even in patients with liver metastases at diagnosis (52% at 15 years)²⁷.
- The unavailability of studies with adequate patient samples and follow-up times comparing surgical and non-surgical patients.
- Biochemical cure rates even lower than in sporadic gastrinoma using standard surgical procedures (up to 0% at 5 years in some studies^{24,28}).

Tumor persistence is also attributed to the multiplicity of gastrinomas and their small size²⁹, which makes complete resection using standard procedures difficult³⁰. Understanding of the distribution in the duodenum of almost all MEN1 and half of the sporadic gastrinomas³¹ has led to duodenotomy with routine duodenal examination being recommended in addition to pancreatic examination in subjects undergoing laparotomy³². In the case reported here, the potential risk of total pancreatectomy and its consequences (in a patient left with only the head of the pancreas after surgery performed 24 years before) led to resection of the growing peripancreatic lesion only, without duodenotomy, being decided upon. Thus, the lack of a duodenal examination, the high probability of gastrinoma location in this region in MEN1^{29,33}, and the poor sensitivity of preoperative techniques for duodenal NETs³⁴ may account for the biochemical persistence of gastrinoma in this patient after surgery. However, even in studies where duodenotomy was routinely performed together with distal pancreatectomy, head examination, and regional lymphadenectomy, cure rates of MEN1 gastrinoma continue to be poor (0% to 33%^{27,35}). As occurs in PHP, only resection of all susceptible tissue has been shown to be possibly curative in a small series of patients undergoing cephalic duodenopancreatectomy, sometimes associated with total pancreatectomy^{36,37}. However, most authors reject routine cephalic duodenopancreatectomy because of its high morbidity rate (higher than 30%) both in the short (fistula, abscess, dehiscence) and long term (endocrine and exocrine insufficiency) and because it makes possible repeat surgery technically difficult². The peripancreatic lesion excised from our patient turned out to be a nodal metastasis from an unresected gastrinoma and exemplifies the high proportion of metastatic adenopathies found in gastrinomas (mainly in those located in the duodenum^{35,36}). Nodal metastases are not usually included in prognostic factors for mortality^{22,38}, unlike liver metastases, which are often the only independent risk factors for mortality in gastrinoma³⁰. Several studies suggest that 15%-30% of patients with MEN1 die due to malignant progression of NETs^{38,39}, and a prospective study reported mortality rates of MEN1 gastrinoma at 8 years of follow-up of 23% and 0% for patients with and without liver metastases respectively⁴⁰. Extrapolating to MEN1 gastrinoma the results of surgery for sporadic gastrinoma, some authors suggest that surgery could delay the occurrence of liver metastases^{41,42} while not achieving a biochemical cure. However, the few

prospective studies of a limited number of MEN1 patients have not been able to show a beneficial effect of surgery for gastrinoma on the incidence of metastasis or mortality¹⁹. Biological variables of both sporadic and MEN1 gastrinomas associated with a greater incidence of liver metastases and higher mortality include primary tumor size (greater than 2-3 cm) and location in the pancreas^{23,38}. The fact that in MEN1 these tumors are usually small and more frequently duodenal in location may account for their less aggressive biological behavior, with higher survival rates^{43,44} as compared to sporadic ones. However, and as occurs in 25% to 30% of sporadic gastrinomas^{22,23}, 14% of MEN1 forms show aggressive behaviour marked by a high growth rate associated with a greater probability of liver metastases and death⁴⁰. While gastrinoma growth in the reported patient was initially slow (it could not be demonstrated in imaging tests between 1997 and 2007 despite increasing gastrin levels), the growing rate of nodal metastasis between 2007 and 2008 and the critical size of 3 cm reached led to lesion resection being indicated. Neither the Ki-67 index (less than 5%) nor its initial progression helped predict such aggressive behavior.

The decision to use somatostatin analogues was based on the potential stabilization of metastatic disease in 40% or more cases⁴⁵, although long-term tachyphylaxis usually occurs⁴⁶ (except in isolated cases)⁴⁷. The benefit of these drugs is greater in NETs which express somatostatin receptors as can be demonstrated by using an octreoscan⁴⁸, and, in particular, in tumors with some degree of differentiation and evolution^{49,50}. Fulfillment of these conditions by our patient and good tolerability of these drugs as compared to other treatment modalities^{51,52} led us to prescribe treatment despite the fact that its prophylactic use (before the occurrence of liver metastases) has not been shown to improve survival in NETs⁵³.

As regards other pancreatic NETs in MEN1, non-functional tumors are even more prevalent than functional tumors (80%-100% in specimens from surgical or autopsy series^{18,54}). In our patient, some of the NETs found in the body and tail during initial surgery, and those found in the head in the second laparotomy, may have been non-functional NETs (immunohistochemistry not available). Surgery for these lesions is also controversial because of their multiplicity and small size³³, which would lead to massive resection. Thus, surgery tends to be performed only when lesions reach a size of 2-3 cm or when rapid growth is observed, in order to slow malignant progression, because some lesions may remain stable for years³⁶. In the case that laparotomy is required to excise functional NETs, some advise resection of both the body and tail of the pancreas because of their association with non-functional NETs^{35,55}.

This case illustrates the diversity of tumors related to this genetic syndrome and their high penetrance, as is shown by their high recurrence in some tissues. Part of the current debate revolves around the decision whether to completely remove some structures in order to prevent recurrence or whether, because of the long-term survival of most patients, to perform more conservative procedures which preserve a high quality of life despite tumor persistence.

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