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Insulinoma as Debut of Multiple Endocrine Neoplasia Type 1: A Case Report

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Abstract

Multiple Endocrine Neoplasia type 1 (MEN1) is a rare autosomal dominant inherited tumor syndrome caused by inactivating mutations of the MEN1 tumor suppressor gene and is characterized by a predisposition to a multitude of endocrine and non-endocrine tumors. It combines the appearance of tumors and / or hyperplasia in the parathyroid, enteropancreatic and adenohypophysis glands, which develop in 90, 30–70 and 30–40% of patients, respectively. We present the case of a 47-year-old female patient with a history of subclinical hypothyroidism. She was admitted to the unit due to persistent symptoms of hypoglycemia. After MRI, a tumor was identified in relation to insulinoma. CT scan of the abdomen with IV contrast revealed a tumor in the adrenal gland. An approach for Multiple Endocrine Neoplasia syndrome was initiated, and an MRI of the skull was requested, ruling out a tumor in the pituitary gland. Patients present with hypercalcemia and hyperphosphatemia, evidenced by parathyroid scintigraphy with a finding of parathyroid hyperplasia. Enucleation of the insulinoma was performed, left supra-adrenalectomy was performed, with histopathological finding of well-differentiated neuroendocrine tumor (WHO 8150/1) and myelolipoma. It was protocolized and electively scheduled for thyroidectomy as well as paratorioidectomy with histopathological finding of mixed pattern parathyroid gland adenomas. Our patient is suspected of being a classic example of MEN1 syndrome with tumors in the 3 defining endocrine organs. When clinical suspicion of MEN1 is high, endocrinologic evaluation with appropriate laboratory studies and specific imaging evaluation of the endocrine organs as described for this patient. Careful multidisciplinary management and follow-up is recommended.

Keywords: Neuroendocrine tumors; Insulinoma; Adrenocortical tumors; Parathyroid hyperplasia; Multiple endocrine neoplasia type 1

Introduction

Multiple endocrine neoplasia type 1 (MEN1) is a rare autosomal dominant inherited tumor syndrome caused by inactivating mutations of the MEN1 tumor suppressor gene and is characterized by a predisposition to a multitude of endocrine and non-endocrine tumors. MEN1 was first described in 1903 by Erdheim and was defined by Underdahl and Werner about five decades later [1].

The genetic basis of MEN 1 is a germline loss-of-function mutation of the MEN 1 gene, which is located on chromosome band 11q13.1. It combines the occurrence of tumors and/or hyperplasia in the parathyroid, enteropancreatic and adenohypophysis glands, which develop in 90, 30–70 and 30–40% of patients, respectively, by the age of 40 years [1,2].

Other endocrine tumors seen more frequently in MEN1 include thymic and bronchial carcinoid tumors, and gastric enterochromaffin-type tumors, each with a penetrance of 2%, 2%, and 10%, respectively, at 40 years of age. Adrenocortical tumors develop in 40% of affected individuals at this age, while pheochromocytomas are rare (<1%) [1].

Non-endocrine manifestations predominantly comprise neoplasms of the central nervous system, including meningiomas, ependymomas, and schwannomas, skin lesions such as lipomas, angiofibromas, and collagenomas, and smooth muscle tumors such as leiomyomas. MEN1 can affect all age groups with an estimated prevalence of 2 per 100,000 and no apparent gender predilection. The clinical diagnosis of MEN 1 is made in patients who have 2 of the 3 most common tumors in MEN1 and in patients with one of the tumors and a family history of MEN 1 [1,3].

Parathyroid Tumors

Hyperparathyroidism (HPT) occurs in 90% of MEN1 patients and is the most common and earliest manifestation of MEN1. Most of its pathological types are adenomas or hyperplasia, which usually affect 2 or more parathyroid glands. The typical age of parathyroid adenomas is 20 to 25 years, which is significantly younger than that of non-MEN1 parathyroid adenomas [4].

The presence of HPT may be clinically asymptomatic and manifest only as biochemical abnormalities. It can also manifest

as hypercalcemia (drowsiness, fatigue, depression, constipation, polydipsia, polyuria), stones in the urinary tract, osteoporosis (pathological fractures) and occasionally peptic ulcers [4].

The initial study in case of suspicion of parathyroid adenoma is performed with ultrasound. Ultrasound also allows us to guide interventional procedures such as fine needle aspiration (FNA), which contributes to the pathological diagnosis of the lesion. Computed Tomography (CT) allows ectopic glands to be located in the mediastinum and behind the trachea. Magnetic Resonance Imaging (MRI) has greater sensitivity than CT for the localization of adenomas but is not usually used in the first line. In nuclear medicine, the use of Sestamibi Scintigraphy has a high sensitivity for the detection of adenomas [2].

Pancreatic Neuroendocrine Tumors

Pancreatic neuroendocrine tumors (pNETs) are a heterogeneous group of neoplasms that arise from the endocrine tissues of the pancreas. pNETs can manifest at any age but are most commonly diagnosed between the ages of 40 and 65 [5].

They appear in 80% of patients. Gastrinoma is the most common neuroendocrine tumor in MEN and is the main prognostic factor due to its malignant potential. Other less common are insulinomas and glucagonomas [2].

pNETs can be classified as functional (F-pNET) or non-functional (NF-pNET), depending on their secretion of various peptide hormones, including insulin, gastrin, glucagon, and vasoactive intestinal peptide (VIP), which gives give rise to various clinical syndromes [5].

Immunohistochemical staining alone is not a defining criterion for tumor classification, as both F-pNETs and NF-pNETs can secrete multiple peptides. NF-pNETs represent the majority (50 to 75%) of pNETs. Although the vast majority of pNETs are sporadic, approximately 10% of all pNETs can also be associated with inherited genetic endocrinopathies [5].

The currently available serum biomarkers are insufficient for diagnosis, but reasonably acceptable for evaluating prognosis and response to treatments during follow-up of pNETs. The morphology, immunohistochemical staining, pathological classification, and clinical staging remain the gold standards for diagnosis [6].

Surgical resection remains the only curative therapeutic option for localized pNETs. However, a debulking operation has also been shown to be effective in controlling the disease [6].

Adenohypophysial Tumors

The incidence of anterior pituitary tumors in MEN1 syndrome varies from 15% to 55% in different series with a mean age of onset in the fourth decade of life, with early cases described at the age of 5 years. Prolactin-secreting adenoma (PRLoma) is the most common pituitary tumor (60%), followed by growth hormone (GH)-secreting adenoma (somatotropinoma or GHoma; 25%), adrenocorticotropic hormone-secreting adenoma (adrenocorticotropin or ACTHoma; 5 %) and NF tumors (10%) [7].

The signs and symptoms of patients with pituitary adenomas are caused by "mass effects" of macroadenomas (mainly NF Adenomas) or secondary to excessive production of pituitary hormones by functioning adenomas [7].

MRI is the test of choice to visualize the pituitary gland. 2 Treatment with dopamine agonists is the first therapeutic option in the case of prolactinomas. In the rest of the hyperfunctioning pituitary adenomas, medical treatment and/or radiotherapy may be necessary after surgery. In non-functioning adenomas that do not compress the optic pathway or produce hormonal deficits, follow-up is usually performed to assess tumor growth, visual impairment or new hormonal deficiency [8].

Adrenocortical Tumors

Adrenal lesions occur in 20 to 55% of MEN1 cases and the majority are adrenal adenomas or hyperplasia. A small fraction of patients with MEN1 develop adrenocortical carcinoma (ACC) [9]. They are usually non-functioning adrenal adenomas and appear in up to 40% of patients with MEN 1 [2].

Initial treatment of adrenal incidentalomas is guided by imaging features, clinical evaluation, and hormonal evaluation. Difficult cases should be discussed in a multidisciplinary expert meeting, especially if malignancy is suspected, if laboratory evaluation suggests a functional adrenal tumor, and if adrenal surgery is considered [10].

In this article, in addition to describing the clinical characteristics of the most common types of tumors within MEN type 1, we will describe the approach, as well as the specific treatment of insulinoma, corticoadrenal tumors and parathyroid hyperplasia.

Case Report

This is a 47-year-old female patient with a history of subclinical hypothyroidism. She is admitted to the unit due to persistent symptoms of hypoglycemia. She begins a diagnostic protocol in the Internal Medicine service under suspicion of Insulinoma. Magnetic Resonance is performed where a nodular lesion is found in the pancreas at the level of the body and tail with dimensions of 26x21x27 mm that reinforces contrast, in relation to insulinoma, CT scan of the abdomen with IV contrast where a tumor is observed in the adrenal gland of heterogeneous density that measures 39x32 mm that shows low density and a negative attenuation coefficient (Figure 1). An evaluation is requested by the General Surgery service. An approach for Multiple Endocrine Neoplasia syndrome was initiated, and MRI of the skull was requested to rule out a tumor in the pituitary gland, in which no abnormalities were found. Patients present with hypercalcemia

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and hyperphosphatemia, evidenced by parathyroid scintigraphy with a finding of parathyroid hyperplasia. Serum insulin values 31.8uU/mL (reference range, 3.21 - 16.32uU/mL). Serum calcium 12.3mg/dL (reference range, 8.2 - 10.2mg/dL), and parathyroid hormone 118pg/mL (reference range, 6.7 - 38.8 pg/mL). Cortisol and Metanephrines normal.

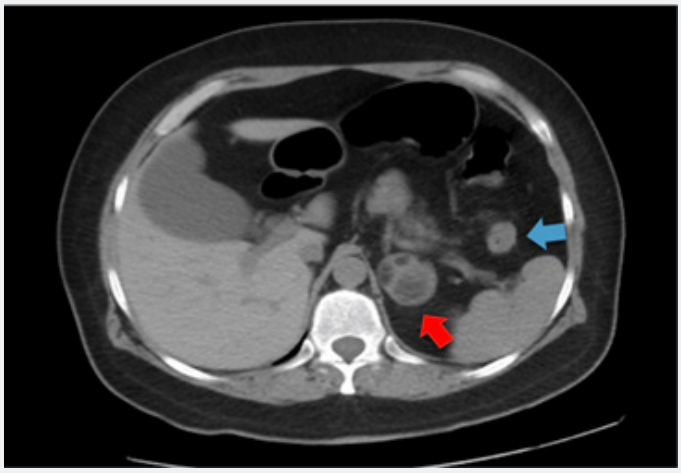

Figure 1: CT scan of the abdomen with IV contrast showing nodular lesion in the pancreas, in relation to insulinoma (red arrow), another tumor is observed in the adrenal gland (blue arrow).

A surgical procedure was performed with a left subcostal approach, identifying Insulinoma on the anterior surface of the body and tail of the pancreas measuring 5 x 4 centimeters, enucleation was performed (Figure 2), and a left supraadrenalectomy was performed, requiring splenectomy for the approach. An adrenal tumor measuring 2.5 x 2 cm identified (Figure 3).

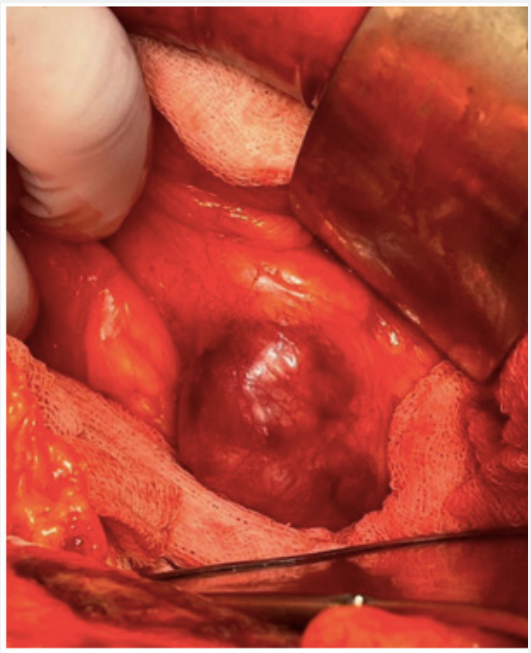

Figure 2: Insulinoma on the anterior surface of the body and tail of the pancreas.

With histopathological findings of 1) Well-differentiated neuroendocrine tumor (WHO 8150/1) and 2) Adrenal gland with nodule corresponding to myelolipoma. In her post-surgical period, the patient presented an adequate evolution, achieving normal basal glucose and insulin levels.

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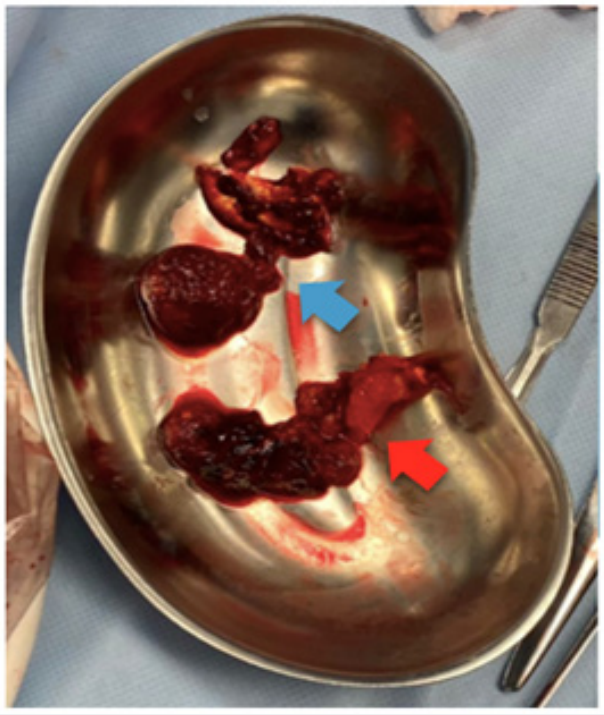

Figure 3: Insulinoma measuring 5 x 4 centimeters (Blue arrow) and an adrenal tumor measuring 2.5 x 2 cm (Red arrow).

It is protocolized and electively scheduled for thyroidectomy as well as paratorioidectomy with histopathological finding of thyroid gland without histological alterations, adenomas of the parathyroid gland of mixed pattern.

Discussion

MEN1 syndrome is also called Werner syndrome, with an estimated prevalence of 2 to 3 per 100,000. The predominant tumors involved in MEN1 include parathyroid, gastroenteropancreatic endocrine, and pituitary tumors. Patients with MEN1 also often develop skin tumors, such as lipomas, collagen tumors, and fibrovascular facial tumors. Other tumor types are associated with MEN1, including adrenal cortex tumors, foregut carcinoids, thyroid tumors, and meningiomas. In recent years, MEN1-related ovarian and uterine tumors have also been reported [4].

Keller et al. [11] mention that although they are not the most common tumors, malignant enteropancreatic neuroendocrine tumors are the main cause of mortality in patients with MEN1. Associated pancreatic islet cell tumors can be functional (hormone-secreting) or non-functional (non-hormone-secreting). Hormone-secreting tumors include gastrinomas (40% incidence), insulinomas (10% incidence), and vipomas and glucagonomas (2% incidence).

According to Gamboa et al. [12] the imaging diagnosis of pancreatic neuroendocrine tumors can be performed with endoscopic ultrasound, which is the most sensitive examination for the detection of small lesions (≤ 10 mm) in asymptomatic patients with MEN 1, with a sensitivity greater than 75%. The use of endoscopic ultrasonography in association with Octreoscan scintigraphy increases the pancreatic tumor detection rate by up to 90%.

Specifically, in insulinoma, laboratory tests will show elevated concentrations of serum insulin (2-20 U/mL or 14.35-143.5 pmol/L) and C-peptide (0.5-2.0 ng/mL or 0.17-0.66 nmol/L). Simple enucleation as a treatment for patients with insulinomas associated with MEN 1 is less likely to be curative, so subtotal pancreatectomy and enucleation of tumors located in the head of the pancreas are the most effective treatment [12].

Van et al. [13] mention the enucleation in patients with MEN1 and a localized insulinoma seems preferable if surgically feasible, as it is associated with a high rate of cure of hypoglycemia, a low risk of recurrent disease, and absence of long-term complications. The feasibility of enucleation depends on the size, location, and relationship of the insulinoma to the main pancreatic duct. In patients with multifocal disease, a more aggressive approach seems advisable based on the current findings, but the location of the insulinoma in these patients is particularly important.

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Although curative resection is the recommended therapy for MEN1-related insulinoma, Radiofrequency Aablation (RFA) has been reported to be a successful treatment. The feasibility, efficacy, and safety of percutaneous, intraoperative, and EUS-guided RFA for pNET was described in ten patients in 2014. Although all patients had complete ablation, serious complications requiring reintervention were observed in three [13].

Adrenal abnormalities associated with MEN1 have been reported since before 1960, and their prevalence has been reported to be as high as 20.4%. Adrenal enlargement in patients with MEN1 was reported in 20.4% of patients and the mean age was younger than the patients with adrenal incidentaloma (46.1 years vs. 55.0 years, respectively). The management of adrenal tumors varies depending on the etiology, associated comorbidities, and patient preferences [14].

Most adrenal myelolipomas are found incidentally, comprising 3.3 to 3.6% of all adrenal tumors in a population, and up to 6 to 6.5% of all adrenal tumors seen in endocrine clinics. In adrenalectomy cohorts, the prevalence of myelolipomas was 4% to 10% overall, and accounted for 15% to 20% in tumors > 4 cm. The prevalence of adrenal myelolipoma in patients undergoing computed tomography (CT) was 0.24%, and in the general population at age 40 years the prevalence has been estimated at 0.32% [15].

Although an association with multiple endocrine neoplasia type 1 (MEN-1) has been suggested in some of the reported cases, complete DNA sequencing did not provide any indication that defects in the MEN-1 gene are responsible for the formation of AML. Low levels of p53 proteins in AML suggest the role of tumor suppressor gene in its tumorigenesis [16].

According to Calissendorff et al. [15] adrenalectomy is usually reserved for a minority of patients with adrenal myelolipomas, most common in patients with large tumors, those with tumor growth, acute hemorrhage, symptoms of abdominal mass effect, or uncontrolled CAH. In several cases, series of surgically treated myelolipomas, the mean tumor size was around 5 to 8 cm. Adrenalectomy was also the treatment of choice in patients with concomitant ipsilateral excess of adrenal hormones. In a series of 305 patients with adrenal myelolipomas, surgery was performed in 37 (12%) patients due to tumor enlargement in a large myelolipoma, symptoms of mass effect, ipsilateral adenoma with excess adrenal hormone, acute hemorrhage, concomitant resection for another reason and to confirm a questionable diagnosis on imaging. Patients undergoing adrenalectomy were younger, had larger tumors with accelerated tumor growth, and a greater likelihood of hemorrhagic changes on imaging than those who were treated conservatively.

Hyperparathyroidism (HPT) is the most frequent involvement of MEN 1. Unlike primary HPT (PHPT), where uniglandular involvement is the most frequent, HPT-MEN 1 is characterized by presenting multiglandular involvement, whose morphological substrate appears to be adenomatous type, since they are mostly monoclonal lesions [17].

Balsalobre et al. [17] mention that due to the characteristics of the syndrome (multiglandular involvement, not synchronous), early surgery would imply less glandular involvement, and therefore more difficulties for complete glandular identification, and perhaps more risk of postoperative hypocalcemia.

On the other hand, late surgery means a greater probability of performing a successful subtotal parathyroidectomy, but at the cost of the patient being exposed to the effects of the disease for longer. Parathyroidectomy should be indicated on an individual basis, both depending on the severity of PHPT and age. Surgical treatment in MEN1's HPT must follow 3 basic criteria: 1) achieve and maintain normal calcium values for as long as possible, avoiding the persistence or recurrence of hypercalcemia; 2) avoid hypocalcemia secondary to surgery, whose consequences in young patients can be worse than their disease itself; and 3) facilitate reinterventions in recurrent disease [17].

Conclusions

Our patient is suspected of being a classic example of MEN1 syndrome with tumors in the 3 defining endocrine organs, including pancreatic insulinoma, parathyroid hyperplasia, and adrenal tumor. When clinical suspicion of MEN1 is high, endocrinologic evaluation with appropriate laboratory studies and specific imaging evaluation of the endocrine organs as described for this patient. Careful multidisciplinary management and follow-up is recommended.

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