CASE REPORT

ACTH Producing Pancreatic Neuroendocrine Tumors in Multiple Endocrine Neoplasia Type 1

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ABSTRACT

Context Cushing syndrome is an uncommon manifestation of multiple endocrine neoplasia type 1 with a possible multifactorial origin pituitary or ectopic adrenocorticothropic hormone producing tumors and adrenal tumors. Adrenocorticothropic hormone producing pancreatic neuroendocrine tumors are also very rare tumors, they represent the less frequent pancreatic neuroendocrine tumor in multiple endocrine neoplasia type 1. **Case report** We present a forty-four-year-old man with primary hyperparathyroidism, adrenal adenoma, pancreatic cyst and an adrenocorticothropic hormone producing pancreatic neuroendocrine tumor without clinical manifestations. Instead the patient had a stable pancreatic cyst since 6 years, only the laboratory analysis revealed an adrenocorticothropic hormone producing pancreatic neuroendocrine tumors hypercortisolism; (111) In-Octreoscan was able to localize the lesion while a magnetic resonance imagingscan performed the characterization. A germ line mutation that affects the splicing of the Menin gene was detected. After a-cephalic duodenopancreatectomy, the biochemical analysis for hypercortisolism is normal. **Conclusion** The patient continues asymptomatic and currently he is included in a regular follow up for multiple endocrine neoplasia type 1 syndrome associated manifestations. An appropriate study and follow up of these patients is necessary to warrantee an early diagnosis of neoplastic lesions and improve their quality of life.

INTRODUCTION

Gastroenteropancreatic neuroendocrine tumors (GEP-NETs) arise from neuroendocrine cells of the diffuse endocrine system from the pancreas or the intestinal tract, representing approximately 2% of all gastroenteropancreatic malignancies [1]. The incidence of these tumors have increased in the Caucasian population from 1.09 (1973) to 5.76 (2007) new cases per 100,000 inhabitants annually [2]. Pancreatic neuroendocrine tumors (PNETs) are a rare cause of ectopic adrenocorticotropic hormone (ACTH syndrome). Ectopic ACTH syndrome (EAS) represents 10–20% of the cases of Cushing's syndrome in western countries and 3.6% of the cases in Japan [3, 4, 5].

GEP-NETs can occur sporadically or as a result of hereditary predisposition syndromes such as multiple endocrine neoplasia type 1 (MEN1) or Von Hippel–Lindau's disease (VHL). MEN1 is a familial cancer syndrome that includes primary hyperparathyroidism, anterior pituitary tumors, adrenal tumors, foregut carcinoid tumors, and GEP-NETs [6, 7]. In MEN1 syndrome, hypercortisolism could be ACTH dependent (pituitary ACTH producing adenomas or ectopic ACTH producing tumors) or independent (adrenocortical tumors) [6].

Pancreatic neuroendocrine tumors (PNETs) are mostly non-functional in MEN1, malignant PNETs are reported to be the most common cause of death in patients with MEN1. The incidence of PNETs in patients with MEN1 varies between 30-80% in different studies [6].

Most PNETs are malignant tumors, metastatic disease is frequently observed at diagnosis, even before the development of Cushing syndrome's features [8]. The ACTH-producing p-NETs metastasize most frequently to the liver, and the goal of treatment is reduction in the size and prevention of the growth of tumor and control of excessive ACTH and/or cortisol production [5].

We report the case of a male patient who presented with PNET developing EAS in the context of a MEN1 syndrome.

CASE REPORT

A Forty-four-year old man was referred to our hospital to discard MEN1 syndrome, he was incidentally diagnosed with hypercalcemia. His personal medical history showed nephrolithiasis, non-functioning 1.2 cm right

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Abbreviations ACTH adrenocorticotropic hormone; GEP-NETs gastroenteropancreatic neuroendocrine tumors; MEN1 multiple endocrine neoplasia type 1; MRI magnetic resonance imaging; PNETs pancreatic neuroendocrine tumors
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adrenal adenoma and two stable pancreatic cysts (<1 cm, located in head and tail respectively) under surveillance since 6 years ago. His father was also diagnosed with nephrolithiasis and primary hyperparathyroidism. The patient was healthy and did not show any symptoms, he was not taking medication. Body mass index was 24 kg/m^2, blood pressure level was 128/69 mmHg. Physical examination was normal and no clinical sign suggestive for hypercortisolism was observed.

Initial endocrine test revealed hypercalcemia (11 mg/dL; normal values 8.9-10.5 mg/dL), elevated urine calcium excretion (29 mg/dL normal values: 25-300 mg/dL) and elevated parathormone (PTH: 155 mg/dL normal values: 10-65 mg/dL). Two parathyroid adenomas were reported in the 99 mTc-sestamibi gammagraphy and osteopenia (T score:-1.1) in the femur neck was also found in DXA (densitometry X ray absorptiometry). Functional test for the adrenal adenoma were repeated: normal potassium, aldosterone/renine ratio and plasma free metanephrines were observed. Pituitary hormones were normal. ACTH levels were increased (29.6 pg/mL; normal values: 7-50 pg/mL) without serum cortisol suppression after 1 mg dexamethasone administration (3.37 – 2.2 mcg/dL; normal value <1.8 mg/dL), elevated midnight salivary cortisol (0.44-0.58-0.81-0.57 mcg/dL; normal values <0.38 mcg/dL), normal urine cortisol level (36.4 mcg/24 hours normal values: 36-137 mcg). Pituitary MRI scan was normal. The desmopressin test for cortisol and ACTH showed any variation in ACTH levels with a 50% serum cortisol increase. Central to peripheral gradient of ACTH after inferior sinus petrosus sampling, before and after 10 mcg of desmopressin, was <2 and <3, respectively. A thoracoabdominal computed tomography (CT) scan was performed, only the two pancreatic cystic lesions and the adrenal adenoma were observed, no changes were reported in these known lesions **(Figure 1a)**. An irregular 3 cm cystic tumor located in the head of the pancreas with late enhancement and cystic degeneration was observed in the MRI scan **(Figure 1b)**. The (111)In-Octreoscan identified a somatostatin receptors positive lesion in the head of the pancreas **(Figure 1c)**.

A cephalic duodenopancreatectomy as well as three gland-parathyroidectomy were performed. The pathology analysis showed a grade 2 PNET (pT2, N0, Mx), with positive immonohisctochemistry to chromogranin, synaptophysin, neuro-specific enolase, somatostatin, glucagon, ACTH and negative to insulin; neither vascular, nerve nor lymph nodes infiltration was reported. Parathyroid glands were hyperplastic; no clear adenoma was identified. The genetic analysis was performed and showed a heterozygous germ line mutation in the Menin gene: c.784-9G>A. The patient did not have offspring, any mutation was found in his parents.

After surgery midnight salivary cortisol and dexamethasone cortisol suppression tests are normal. Currently the patient continues asymptomatic and is under surveillance by the endocrinologist team.

DISCUSSION

We present a very rare case of asymptomatic EAS due to a PNET in a patient with a MEN1 syndrome; an incidental hypercalcemia combined with pancreatic cyst lesions and adrenal adenoma suggested a possible family syndrome. An appropriate diagnosis, treatment and follow up of GEP-NETs in MEN1 patients are essential to warrantee an appropriate quality of life for these patients. The incidence of primary hyperparathyroidism is 99%, pituitary adenomas 47% and pancreatic tumors 67%, for this reason a biochemical and radiological screening in individuals at high risk of developing MEN1 is necessary [9].

MEN1 is an autosomal dominantly inherited disease that is caused by germline mutations in the MEN1 gene which is a tumor suppressor gene for endocrine tissues [10], is characterized by the occurrence of tumors involving two or more endocrine glands in a single patient [9]. The incidence of MEN1 ranges 1–18% in patients with primary hyperparathyroidism, 16–38% in patients with gastrinomas, and <3% in patients with pituitary tumors. The disorder affects all age groups (age range: 5-81 years old). This disorder has a high degree of penetrance, clinical and biochemical manifestations will develop in 80% and >98% of patients by the fifth decade respectively [11, 12].

More than 450 different germline MEN1 mutations have been identified, missense mutations have been reported in about 20% of the cases [13]. Both type of mutations result in reduced levels of protein due to proteolytic degradation via the ubiquitin–proteasome pathway [14]. MEN1 mutational analysis is helpful in clinical practice allowing the confirmation of the clinical diagnosis, the identification of affected family members who will require screening for tumor detection and early/appropriate treatment [9]. According the Online Mendelian Inheritance in Man (OMIM) report, the germ line mutation c.784-9G>A is a single nucleotide variant localized in 11q13.1 chromosome which generates splicing modifications with an intron variant in the Menin gene. Although the patient did not have clinical sign or symptoms, laboratory tests revealed a clear ACTH dependent hypercortisolism which completely disappeared after surgery.

MEN1-related NETs are an important cause of morbidity and presently malignant duodenopancreatic NETs and thoracic NETs are the main cause of MEN1-related death [15]. GEP-NETs include functioning and non-functioning tumors, depending on their capacity on secreting peptide hormones; in the MEN1 syndrome, synchronous GEP-NETs may secrete different hormones based on immunohistochemistry [16]. GEP-NETs are classified according to the European Neuroendocrine Tumor Society/World Health Organization grading system into three grades based on proliferation rate [8]. In patients with MEN1-related GEP-NETs, estimated 10-year survival is 75% [17]; the risk of death seems to differ between the various subtypes, with the rare functioning tumors presenting the highest risk followed by non-

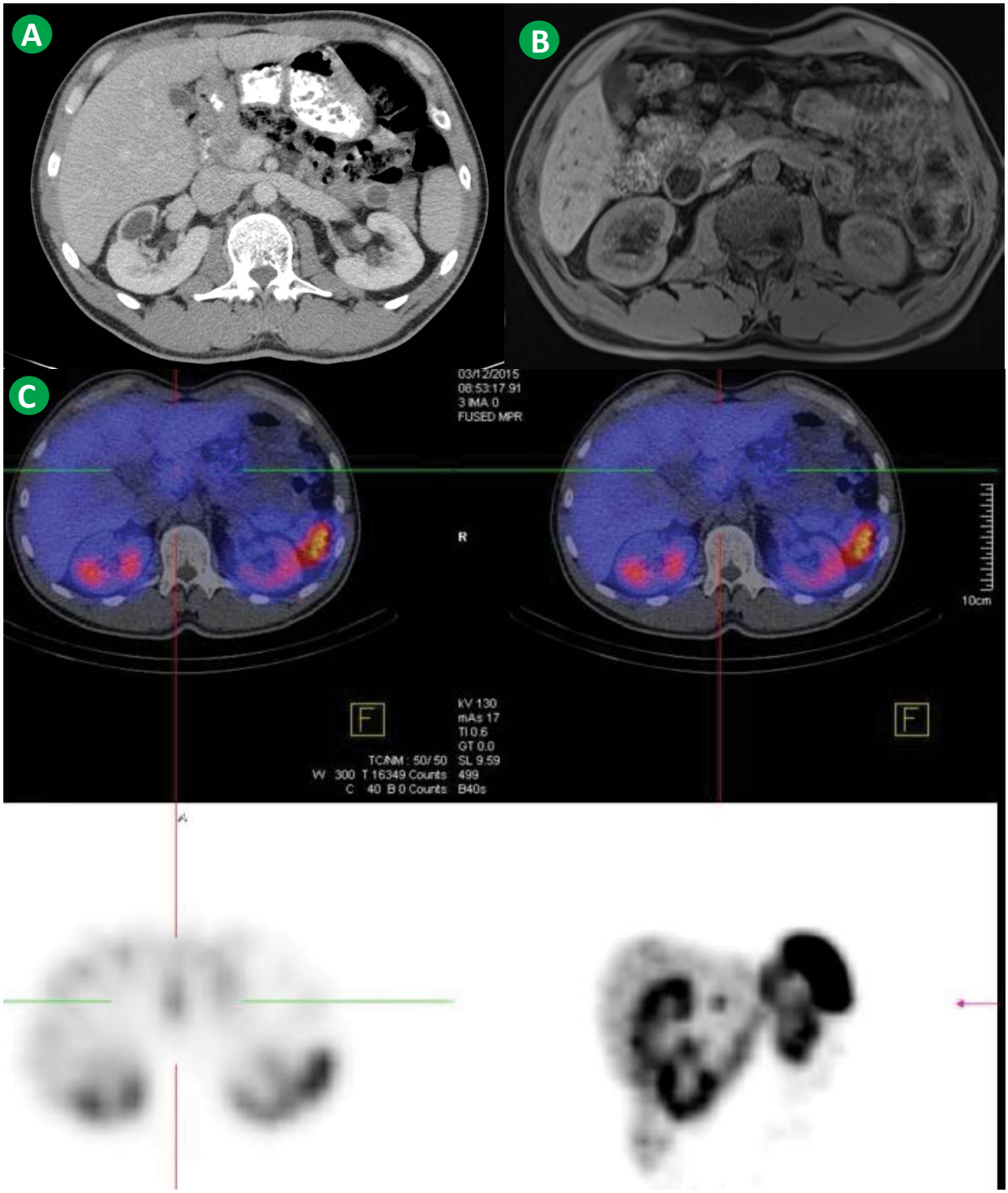

Figure 1. Imaging diagnosis in ACTH producing PNET. **(a)** CT scan shows two stable pancreatic cystic lesions; **(b)** Cystic tumor located in the head of the pancreas with late enhancement and cystic degeneration in the MRI; **(c)** (111)In-Octreoscan with a somatostatin receptors positive lesion in the head of the pancreas.

functioning PNETs and gastrinoma [18]. The clinical onset in patients with genetic predisposition occurs earlier; in several cases, GEP-NETs are usually multiple in contrast to the mostly solitary sporadic PNETs [2]; at pathology, all MEN1 patients have multiple micro-adenomas (PNETs <5 mm without clinical syndrome) dispersed throughout the pancreas associated with one or more NETs ≥5 mm [10, 19].

Due to the high prevalence and morbi/mortality of GEP-NETs in MEN1 syndrome, clinical guidelines recommend a regular screening including, as a minimum, an annual plasma biochemical evaluation of a fasting gastrointestinal tract hormone (gastrin, glucagon, vasointestinal polypeptide, pancreatic polypeptide, chromogranin A, and insulin with an associated fasting glucose level) [9]. There is no consensus for radiological screening, annual pancreatic and duodenal visualization with magnetic resonance imaging (MRI), computed tomography (CT), or endoscopic ultrasound has been suggested [9].

Non-functioning PNETs are the most common tumor in MEN1, followed by gastrinomas, insulinomas, glucagonomas and VIPomas. Some case series of NETs

in MEN1 syndrome patients have been reported, predominately ACTH-producing NETs of the thymus have been reported [20]. ACTH producing PNETs is the less frequent functioning PNET in MEN1 [21], ranging 0-5% [22], but it has been observed in 5–31% of the sporadic cases [18].

Cushing syndrome (CS) is an uncommon manifestation in MEN1. In this syndrome, 5–10% of pituitary adenomas secrete ACTH [6, 23, 24], some GEP-NETs and thymic carcinoids may also produce ACTH; at the same time, adrenocortical functional tumors (benign and malignant neoplasms) are non-ACTH dependent causes for CS [7, 25].

PNETs with ACTH production are very rare tumors, they represent less than 1.2% of all PNETs in the Japanese population [26] and cause 16% of EAS in the western countries. Hormone secretion could occur since the diagnosis, but hormonal secretion after relapsed disease as well as other hormones cosecretion have been also described [27, 28].

Bronchial carcinoids are the most frequent cause of EAS [29]; small cell lung carcinoma, pancreatic, thymic tumors and thyroid medullary carcinoma may produce ectopic ACTH in a lower frequency [5]. The majority of patients are middle-aged women with limited comorbid diseases [30]. These indolent tumors are slower growing, and their localization often precedes ACTH secretion and the Cushingoid phenotype; variations in clinical course can be ascribed to aggressive transformation of the tumor upon disease recurrence or liver metastases [5].

Around 90% of EAS PNETs are malignant; liver metastases are often identified at the initial diagnosis, the prognosis of these tumors usually is poor due to a rapidly progressive disease [5, 31]. The 5 year-survival rate in metastatic PNETs is around 16% [5].

Clinical presentation of ectopic ACTH syndrome (EAS) varies from nonspecific symptoms to diabetic ketoacidosis, hypertensive crisis or psychotic presentation, but in general, is EAS an aggressive disorder [32]. An acute syndrome is characterized by a rapid onset of hypertension, weakness, edema, hypokalemia, glucose intolerance, anorexia, and weight loss, this clinical presentation is typical of small cell lung carcinoma [3, 33]. A chronic syndrome presentation could be clinically indistinguishable from pituitary-dependent hypercortisolism presenting with plethora, truncal obesity, buffalo hump, and red striae [33].

Preoperative imaging and localization are essential before considering surgical resection of these tumors. The imaging modalities most commonly used are triple phase multidetector CT scan and MRI with gadolinium contrast. PNETs are usually hyperenhancing masses in the arterial phase of the scan (both primary and metastatic lesions) due to their hypervascular nature. As most pancNETs express a high density of somatostatin receptors (specifically subtypes 2 and 5), indium-111-labeled somatostatin receptor scintigraphy (SRS) is an effective localizing tool in this disease; (^{68}Ga) DOTA-TATE PET may be useful not only in diagnosis bur also in monitoring response to treatment with peptide receptor radionuclide therapy (PRRT) and locoregional ablation of liver metastases [34, 35].

In case of located disease, surgery is the best treatment option, radical surgery is the only curative treatment for PNETs [31]; the goals of surgery include resection of primary tumor for potential cure and prevention of malignant progression [36]; because more than 50% of patients with PNETs have metastatic and multifocal disease at presentation, they are rarely cured by surgery, hence, the goal of surgery in this group of patients is to reduce the risk of metastases and improve survival [37].

When surgery is not possible, ACTH and/or cortisol normalization for controlling the symptoms is the most preferred treatment goal, patients who are reasonable surgical candidates are likely to benefit from adrenalectomy [29]. Treatment options for metastatic tumors include transarterial chemoembolization, somatostatin analogues therapy, interferon, even liver transplantation or systemic chemotherapy [5]. According to guidelines, chemotherapy may be used for inoperable or metastatic pancreatic NET. Sunitinib and everolimus may be considered for patients with advanced (inoperable or metastatic) progressive well-differentiated PNETs [9].

Our patient also was diagnosed from a non-functioning adrenal adenoma. The incidence of asymptomatic adrenocortical tumors in patients with MEN1 is reported to be 20 –73% [38]. Most of these tumors, which include cortical adenomas, hyperplasia, multiple adenomas, nodular hyperplasia, cysts, or carcinomas, are non-functioning. Less than 10% of enlarged adrenal glands have hormonal hypersecretion [9]. The treatment of MEN1-associated adrenal tumors is similar to that for non-MEN1 adrenal tumors. Surgery is indicated for functioning tumors (primary hyperaldosteronism or ACTH independent hypercortisolism), and nonfunctioning tumors with atypical features or significant growth over a 6-month interval [9], for this reason, any surgical management was performed in our patient.

In the last years we have observed significant advances in the diagnosis and management of MEN1 patients; the early detection of tumors through periodic screening programs has represented an improvement in management and quality of life. However, according to guidelines, the optimal treatment of MEN1-associated tumors still remains to be defined because there is a paucity of clinical trials examining the outcomes of specific therapies for the treatment of MEN1- associated tumors [9]. However, the recruitment of appropriate numbers of MEN1 patients for clinical trials may not be possible from single national centers, for this reason, it is important to improve the development of national and international MEN1 registries [9].

CONCLUSION

In conclusion, we have reported a patient with EAS PNET with an indolent clinical course in MEN1 syndrome

context; the purpose of this article is to highlight the usefulness of an early diagnosis and treatment strategy in these patients. Therefore, the management of PNETs especially in familial cancer syndromes requires an individualized care and follows up.

Conflict of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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