Article published online: 2022-07-07

CASE REPORT

Ectopic ACTH Syndrome Caused by Hepatic Metastases from Previously Non-Functional Pancreatic Neuroendocrine Tumor

Rafik R El Mehdawi[1,2], Abdulwahab M Elbarsha[1,2], Najat Buzaid[1,2], Adel Attia[1,3], Maisoon El Hemri[2]

[1]Department of Medicine, Faculty of Medicine, University of Benghazi, Benghazi, Libya.
[2]Department of Medicine, Benghazi Medical Center, Benghazi, Libya.
[3]Department of Hematology and Oncology, Benghazi Medical Center, Benghazi, Libya.

Corresponding author: Dr. Abdulwahab M. Elbarsha Email: elbarsha@hotmail.com
Published: 01 July 2016
Ibnosina J Med BS 2016;8(4):120-124
Received: 28 May 2016
Accepted: 10 June 2016
This article is available from: http://www.ijmbs.org

Abstract

Background: Pancreatic neuroendocrine tumors (NETs) are rare; representing less than 10% of all primary pancreatic tumors. The minority of these tumors are functional producing a clinical syndrome according to the hormone secreted. ACTH production by pancreatic NETs is rare and even rarer, it occurs from liver metastasis later in the course of the disease. **Case Report:** We report a case of a 30-year-old Libyan man who presented with Cushing's syndrome due to ectopic ACTH production from liver metastases of a pancreatic NET. The pancreatic NET was diagnosed 7 years previously when it was considered a non-functional at the time of diagnosis; the tumor was resected completely then. In the current presentation there was no evidence of the primary tumor but multiple liver metastases were present. **Conclusions:** This report highlights the fact that initially non-functional pancreatic NETs may present later with a functional hormonal syndrome either from the primary tumor itself or from its metastatic secondary tumors elsewhere.

Keywords: Pancreas; neuroendocrine tumors; ACTH; Cushing's syndrome.

Introduction

Neuroendocrine tumors (NETs) are epithelial neoplasms with predominant neuroendocrine differentiation (1). They are characterized by having somatostatin receptors on the surface of their cells and by being hypervascular (2). Pancreatic NETs are rare neoplasms and represent about 2% to 10% of all primary pancreatic tumors (1). However, due to the advances in imaging techniques, the number of pancreatic NETs found as "incidentalomas" has increased. Up to 75% of pancreatic NETs are non-functional neoplasms. The peak incidence of non-functional pancreatic NETs is during the fifth decade, with equal sex distribution (1). Functioning tumors are those in which there are clinical symptoms related to peptide/hormone overproduction.

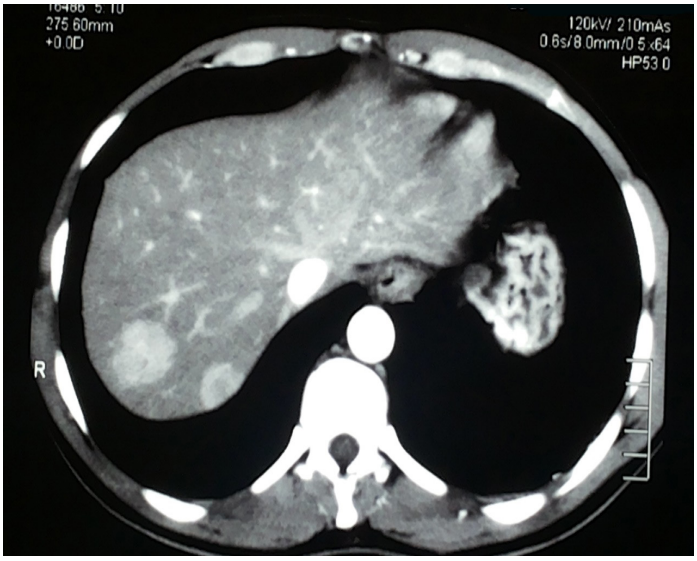

Figure 1. Enhanced CT of the liver showing liver metastasis of the pancreatic neuroendocrine tumor.

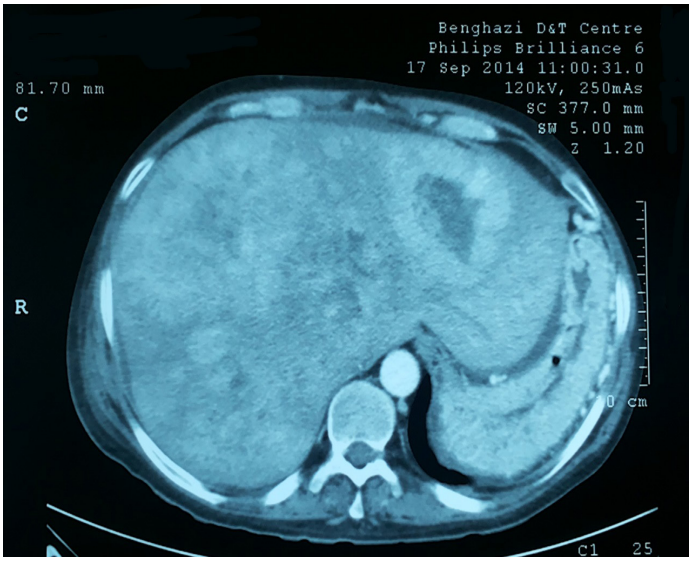

Figure 3. Enhanced CT of the liver showing multiple hypervascular liver metastasis of the pancreatic neuroendocrine tumor

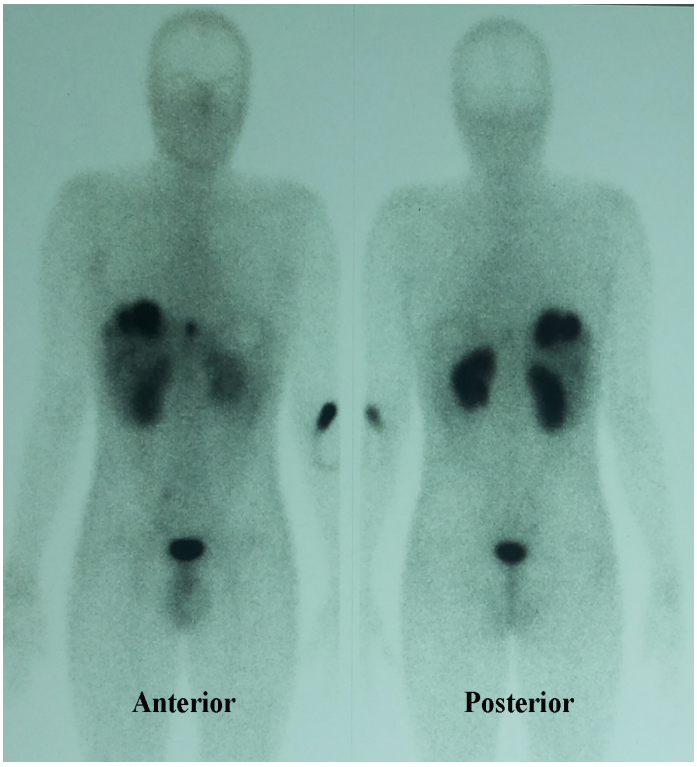

Figure 2. Whole-body Octreotide Scan image demonstrating abnormal hepatic tracer accumulation compatible with liver metastases of the pancreatic neuroendocrine tumor.

Tumors that do not produce specific symptoms should be considered non-functioning tumors even though they may secrete some pancreatic polypeptide (3). Ectopic ACTH secretion from functional pancreatic NET is rare, and it is even so with non-functional tumors. There are very few cases in the literature reporting such evolvement into ACTH-secreting functional tumors (4). We report here a case of a young Libyan man with a rare non-functional pancreatic NET that later during the course of the disease started de novo secretion of ACTH from liver metastases.

Case Report

We report a case of a 30-year-old man who presented with a 4-month history of generalized fatigability, generalized body swelling, and significant weight gain. He had been diagnosed with diabetes mellitus 4 months previously and developed hypokalemia 1 month later. He has had primary epilepsy since childhood for which he is treated with sodium valproate 500 mg three times a day. He was diagnosed to have a non-functional pancreatic neuroendocrine tumor 7 years previously, having presented with abdominal pain and weight loss. Abdominal computed tomography (CT) at that time had demonstrated tumor at the tail of the pancreas, for which the patient underwent spleno-caudal pancreatectomy with segmental resection of the adjacent transverse colon. Immunohistochemistry of the pancreatic specimen stained positive for chromogranin, neuroendocrine-specific enolase, and synaptophysin, with a Ki-67 index of < 5% and mitotic count > 2/10 high-power fields (HPF) confirming the diagnosis of grade 2 pancreatic neuroendocrine tumor (ACTH staining was not performed). One year later, a follow-up abdominal CT scan

was reported as normal and the residual portion of the body and head of the pancreas was visualized with no evidence of recurrence or metastasis. Three years subsequently, he was admitted with sub-acute intestinal obstruction due to adhesions, and abdominal CT-scan showed multiple liver lesions suggestive of metastases (Figure 1). A subsequent octreoscan showed increased uptake at these liver lesions (Figure 2) .The chromogranin A serum level at that time was 185 ng/ml (0-95 ng/ml). The patient received four cycles of palliative chemotherapy (Etoposide 100mg/m^2 Day 1-3, and Cisplatin 75mg/m^2 Day 1 regimen). Re-evaluation abdominal CT-scan after finishing four cycles showed regression of the size of liver metastases. One year later he underwent two sessions of transarterial chemoembolization (TACE) using Doxorubicin and Cisplatin with a partial response, followed by monthly Octreotide 20mg (somatostatin analog) and daily Everolimus 10mg (m-Torkinase inhibitor tablet). Two years later, he presented with Cushingoid features with centripetal obesity, plethoric moon face, and proximal myopathy, and his blood pressure was high. Biochemical investigations revealed serum potassium 2.7 mmol/l, glucose 345 mg/dl, and significantly elevated random serum cortisol of 1,555 nmol/l (171-536 nmol/l) and serum ACTH 660 pg/ml (7.2-63.3). An overnight low-dose dexamethasone suppression test showed non-suppressible serum cortisol, and the cortisol level after an 8 mg dexamethasone suppression test also was non-suppressible at 1552 nmol/l. Pituitary magnetic resonance imaging was normal and abdominal CT-scan showed multiple hypervascular liver metastases and bilaterally hypertrophied adrenals with no evidence of local recurrence (Figure 3). Based on these results, a diagnosis of functioning metastatic pancreatic NET with ectopic ACTH production causing Cushing syndrome was made. The patient was treated with ketoconazole 200 mg tds to control the hypercortisolemic state and was referred back to his medical oncologist for opinion regarding palliative chemotherapy.

Discussion

Pancreatic NETs are classified according to the predominant hormone they secrete, and the resulting clinical syndrome, into insulinomas, gastrinomas, glucagonomas, VIPomas and somatostatinomas, with insulinomas and gastrinomas being the most common functional pancreatic NETs. With the exception of insulinomas, pancreatic NETs are commonly malignant. However, about 75% of pancreatic NETs are actually non-functional (1). The clinical features of pancreatic NETs vary from the mass effects of the primary tumor to specific primary functional syndromes according to the primary secreted hormone. Non-functional pancreatic NETs usually present late as large tumors, with signs and symptoms related to the tumor mass itself (1). Very rarely, a secondary functional syndrome such as carcinoid syndrome or ectopic ACTH syndrome might evolve due to de novo hormone secretion during the course of the disease, with a median delay of 19 months (range: 7-120 months); 92% of these new functional syndromes could be attributed to liver metastases (5).

The time lag in our patient from the diagnosis of the primary tumor to the development of clinical features of Cushing's syndrome was almost 80 months (6.6 years). Obviously, the longer the patient lives the more likely a new hormonal syndrome may develop. With the newer and more effective therapies currently available, patients are expected to live long enough to develop a second or even a third hormonal syndrome. This requires an increased awareness of this possibility to diagnose and treat these new clinical syndromes and hopefully reduce the morbidity and mortality of these patients. Somatostatin-receptor scintigraphy has a 90% sensitivity and 80% specificity for pancreatic neuroendocrine tumors and is a routine investigation for both primary tumors and metastases1. The minimal biochemical investigations include studies for specific hormonal activity as well as the general tumor marker for NETs, chromogranin A and pancreatic polypeptide.

The diagnosis of pancreatic NETs is primarily a pathological one using a conventional hematoxylin and eosin stain and immunohistochemical staining with chromogranin and synaptophysin (6). Determination of the mitotic index by counting 10 HPF, and calculation of the Ki-67 index by immunohistochemistry, are essential for precise diagnosis and categorization (1,3). The tumors are classified according to the World Health Organization system into three categories: grade 1 (benign NET), grade 2 (low-grade malignancy), and grade 3 (high-grade malignancy) (7). Most cases are grade 2, including our patient. The prevalence of concurrent metastases at the time of diagnosis of non-functional pancreatic NETs is 75% (8). Our patient did not show evidence of tumor metastasis at the time of diagnosis; however, metastases showed up 4 years later. Non-functional pancreatic NETs are recognized as part of multiple endocrine neoplasia type 1 (MEN-1), von Hippel-Lindau (VHL) disease, and neurofibromatosis type I, and have also been reported in patients with tuberous sclerosis

(9). Yet, germline DNA testing is only necessary when the clinical situations strongly suggest MEN-1 or VHL disease (1).

Surgery is the mainstay of treatment, and the extent of surgery depends on the size, localization, and WHO grade of the tumor. Small, non-malignant, easily accessible tumors can be treated by local limited resection (enucleation or middle pancreatectomy), while in localized but larger tumors (> 2 cm), aggressive surgery is indicated and resection of adjacent organs such as the stomach, colon, kidney, and adrenal gland is sometimes required (10). Resection of liver metastases may be justified if at least 90% of the tumor mass can be reduced. This kind of surgery should only be performed in experienced centers. Elective (chemo-) embolization is a type of palliative therapy that aims at reduction of hepatic lesions and is mainly indicated in the management of untreatable functionally active liver metastases without manifestation of extrahepatic disease, like our patient's situation (11). Liver transplantation is another option in a patient without extrahepatic metastases when all other therapeutic options are unsuccessful. Biotherapy with somatostatin analog can be used as first-line medical therapy in cases of progressive tumors with a slow proliferation index. This approach may lead to disease stabilization in about 50% of patients (12). Interferon alpha is another option; however, the safety profile is better with somatostatin analogs than with interferon. Conventional chemotherapy with streptozotocin, 5-FU, doxorubicin, cisplatin, or etoposide is indicated as medical therapy in progressive tumors if biotherapy has failed (1).

Overall, the 5-year survival of patients with non-functional pancreatic NETs is between 30% and 63%, with a median survival from diagnosis of 72 months (1). At the time when this report was written, our patient had already passed 87 months of survival since diagnosis. The prognosis depends on the presence or absence of metastases and histopathological grade1. The clinical course of patients with metastatic NET is very variable. Patients with indolent tumors may remain symptom-free for years, while others will develop symptomatic disease, either from tumor bulk or peptide hormone hypersecretion (1). However, in one report, 91.6% of those patients who developed a second hormone syndrome have died, as their clinical status deteriorated after they developed the new clinical syndrome (5). Follow-up investigations aim to clarify whether more therapy is indicated or effective. Clinical examination, serum chromogranin A level, and radiological investigations all are recommended (1).

In conclusion, one should be aware of the possibility of evolution in tumor functionality during the course of the disease, particularly with the newer and more effective therapies that are currently used, which lead to increased life expectancy of patients, allowing development of a second or even a third hormonal syndrome. Moreover, patients who develop a second hormonal syndrome usually require more aggressive treatment as their clinical status may deteriorate as a result of the new syndrome.

References

1. Falconi M, Plöckinger U, Kwekkeboom DJ, Manfredi R, Körner M, Kvols L, et al. Well-differentiated pancreatic nonfunctioning tumors/carcinoma. Neuroendocrinology 2006;84:196-211.
2. McKenna LR, Edil BH. Update on pancreatic neuroendocrine tumors. Gland Surg 2014;3(4):258-75.
3. O'Toole D, Salazar R, Falconi M, Kaltsas G, Couvelard A, de Herder WW, et al. Rare functioning pancreatic endocrine tumors. Neuroendocrinology 2006;84:189-95.
4. Rajeev SP, McDougall S, Terlizzo M, Palmer D, Daousi C, Cuthbertson DJ. Evolution in functionality of a metastatic pancreatic neuroendocrine tumour (pNET) causing Cushing's syndrome: treatment response with chemotherapy. BMC Endocr Disord. 2014;14:70.
5. Wynick D, Williams SJ, Bloom SR. Symptomatic secondary hormone syndromes in patients with established malignant pancreatic endocrine tumors. N Engl J Med 1988,319:605-07.
6. Wiedenmann B, Franke WW, Kuhn C, Moll R, Gould VE. Synaptophysin: a marker protein for neuroendocrine cells and neoplasms. Proc Natl Acad Sci USA 1986;83(10):3500-4.
7. Rindi G, Arnold, R, Bosman FT, Capella C, Kilmstra DS, Kloppel G, et al. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: Bosman FT, Carneiro F, Hruban RH, Theise ND. (Eds.); WHO Classification of Tumours of the Digestive System, 4th. IARC Press: Lyon, France, 2010; p:13-4.
8. Mignon M. Natural history of neuroendocrine enteropancreatic tumors. Digestion 2000;62(suppl 1):51-8.
9. Francalanci P, Diomedi-Camassei F, Purificato C, Santorelli FM, Giannotti A, Dominici C, et al. Malignant pancreatic endocrine tumor in a child with tuberous sclerosis. Am J Surg Pathol 2003;27:1386-9.

10. Hellman P, Andersson M, Rastad J, Juhlin C, Karacagil S, Eriksson B, et al: Surgical strategy for large or malignant endocrine pancreatic tumors. World J Surg 2000;24:1353-60.
11. Proye C. Natural history of liver metastasis of gastroenteropancreatic neuroendocrine tumors: place for chemoembolization. World J Surg 2001;25:685-8
12. Panzuto F, Di Fonzo M, Iannicelli E, Sciuto R, Maini CL, Capurso G, et al: Long-term clinical outcome of somatostatin analogues for treatment of progressive, metastatic, well-differentiated enteropancreatic endocrine carcinoma. Ann Oncol 2006;17:461-6.