Neuroendocrine Tumor, diagnostic difficulties

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Abstract

Ectopic adrenocorticotropic hormone (ACTH) secretion is a rare disease.

A 51 years old woman, with a Cushing syndrome secondary to ectopic ACTH secretion, diagnosed in 2009, with mediastinal lymphadenopathy, whose biopsy was compatible with lung small cell carcinoma, staged as IIIB using TNM classification. No other lesions were found in patient study. The patient was submitted to chemotherapy, associated to ketoconazole 200 mg twice daily, with partial remission of both conditions. Three years later was admitted with an aggravation of Cushing syndrome. There was no evidence of progression of pulmonary disease. A cystic lesion in the pancreatic uncinated process was found by abdominal CT scan and with avid uptake by DOTANOC PET discreet in anterior mediastinal lymphadenopathy. Biopsy of pancreatic mass revealed a neuroendocrine tumor. Pulmonary masses were biopsied again and was in favor of neuroendocrine tumor. It was assumed the diagnosis of pancreatic neuroendocrine tumor with mediastinal metastasis. The patient initiated lanreotid (120 mg, monthly, subcutaneous) in association with ketoconazole. After 5 months of therapy, patient died with sepsis secondary to pneumonia.

Neuroendocrine tumours are rare, difficult to diagnose and with poor prognosis when associated with ectopic ACTH secreting Cushing syndrome.

Keywords: Neuroendocrine tumor. Cushing syndrome. Small cell lung cancer. DOTANOC PET. Ectopic ACTH secreting tumour

Palabras clave: tumor neuroendocrine. Síndrome de Cushing. Cáncer de pulmón de células pequeñas. DOTANOC PET. Tumores ectópicos ACTH secretoras

Introduction

Ectopic adrenocorticotropic hormone (ACTH) secretion is responsible for 12-17% of cases of Cushing's syndrome. It is a rare disease with a reported incidence of 0.1 per million per year.[1]

Ectopic ACTH-producing tumours are aggressive and present diagnostic and management challenges with often poor prognosis.[2] Hypercortisolism is particularly severe in these cases and may manifests itsef as weight gain, severe fatigue, muscle weakness, high blood pressure, depression, cognitive impairment, purple striae, easy bruising, hyperpigmentation loss of libido, diabetes, hirsutism, acne and menstrual disorders, it can also lead to significant immune suppression, which may predispose patients to the development of infections. [2,3] The ectopic source of ACTH is located in the lungs in over 45% or tumours. Small cell lung carcinomas are responsible for about 20% of cases, although ectopic ACTH hypersecretion occurs in only 0.5-2% of these tumours. Thymus (11%) and pancreas (8%) are the next most common affected organs.[1] Identification of the source of ectopic ACTH production remains one of the main difficulties in these cases.

We present a 51 years old woman with an ACTH-secreting tumour to demonstrate the difficulties of neuroendocrine tumours diagnosis and management.

Case Report

We present a 51 years old woman, with a Cushing syndrome ACTH dependent since 2009. Initially she presented diabetes, hypertension, central obesity, full moon face, osteoporosis, chronic hypokalemia and depression disorder. Laboratory findings revealed elevated levels of ACTH and cortisol. Cerebral magnetic resonance presented a small nodule of 6 mm in pituitary gland compatible with pituitary microadenoma. She was submitted to surgical removal of microadenoma. After surgery she maintained elevated ACTH and cortisol levels. In 2010 she presented an elevated 8 am Plasma Cortisol [57,5 micrograms/dL (N 6,4 – 19,4)] with elevated plasma ACTH [409 pg/mL (N 0-46)]. Chest Computerized tomography revealed mediastinal lymphadenopathy; transbronchial biopsy was compatible with lung small cell carcinoma, staged as IIIB using TNM classification. Staging of the tumour did not reveal any other lesion associated with metastasis outside the thoracic region. The patient was proposed to chemotherapy with cisplatin and etoposide, associated to ketoconazole 200 mg twice daily, having partial remission of the carcinoma and the Cushing syndrome, although ACTH was still elevated (344 micrograms/mL)

In 2012 she suffered a relapse of hypercortisolism symptoms under ketoconazole treatment, such as mental disorders, diabetes, and ionic disturbances. Diabetes was difficult to control, in association with delirium and relapsing hypokalemia after interrupting intravenous reposition.

During hospital admission, the patient presented a fluctuating haemoglobin level, from 8.7 to 13.3 g/dL, without iron deficit or blood loss besides several large bruises; She also had moderate thrombocytopenia from 57,000 to 186,000 per microliter.

Thorax Computerized tomography (CT) and Positron Emission Tomography (PET) scan did not show progression of the pulmonary disease. However, abdominal CT scan found a new cystic lesion in the pancreatic uncinate process with 38 x 30 mm, conditioning extrinsic compression of the biliary duct, which was confirmed in echoendoscopy.

DOTANOC PET scan showed avid uptake in the pancreatic tail and discreet in anterior mediastinal lymphadenopathy. (Figure 1)

In 2012 a CT guided biopsy of the pancreatic mass was achieved, revealing a neuroendocrine tumor and immunohistochemistry revealed that this lesion produced ACTH.

It was decided to repeat pulmonary masses biopsy. This time, histology and immunohistochemistry were in favor of neuroendocrine tumor. (Figure 2)

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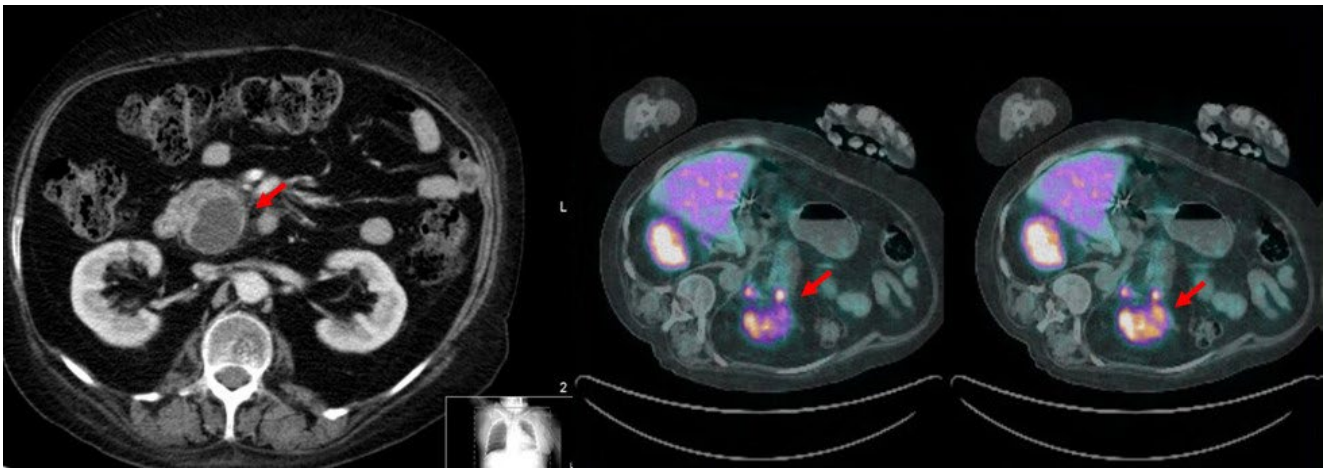
Figure 1. CT scan and DOTANOC PET of pancreatic mass (arrow).



The diagnosis was assumed of a pancreatic neuroendocrine tumor with mediastinal metastasis (Stage IIIb). Due to all the comorbidities, she was refused for surgical treatment of the primary tumor and initiated lanreotide (120 mg, monthly, subcutaneous) in association with ketoconazole. After 5 months of therapy, the patient died with severe sepsis secondary to pneumonia.

Discussion

With an insidious presentation, depending on hormone activity and complex regulation systems, neuroendocrine tumours present always a challenge in diagnosis and treatment. [4]

Histology can lead us to inaccurate diagnosis, being responsible for unnecessary procedures and delaying proper treatment. Clinical relapse with stable pulmonary disease made us suspect another cause to ectopic ACTH secretion. A small number of cases of incorrect histological diagnosis are published, more often for carcinoid or large cells tumours of the lung.[5] Small biopsy samples may limit diagnosis because occasionally there is not enough material to all immunohistochemical profile necessary to a correct diagnosis.[6]

Hypercortisolism manifestations such as those previously described made us investigate the underlining disease, questioning pulmonary cancer progression or another ACTH producing tumour.

After lung and thymus, pancreas is the most common place for ectopic ACTH-producing tumours, directing our clinical investigation. Due to thrombocytopenia, an endoscopic biopsy was unable.

^{68}Ga-DOTA-NOC-PET, based in a somatostatin analogue with affinity to somatostatin receptor 2, can be helpful detecting neuroendocrine tumours, with more accurate results than older nuclear medicine methods such as ^{111}In-DPTA-octreotid (OctreoScan ®).[7] In this case, it helped us confirming neuroendocrine origin of the pancreatic mass that was later discovered, not visualized in initial exams, and its relation to pulmonary nodules due to the same imaging profile with this technique. Biopsy, in addition to this information, confirmed the diagnosis. This fact explains why the patient remained alive for so long after the supposed initial diagnosis of small cell lung cancer.

Due to the extension of the disease, and lobal health status of the patient, surgical treatment was not possible. Ketoconazole alone had been unsatisfying after a long time of treatment. Lanreotide, a somatostatin analogue, was associated with significant progression-free survival among patients with some types of neuroendocrine tumours.[8] In this patient, we associated lanreotide 120 mg monthly expecting to improve control of endocrine manifestations and prolong life expectancy.

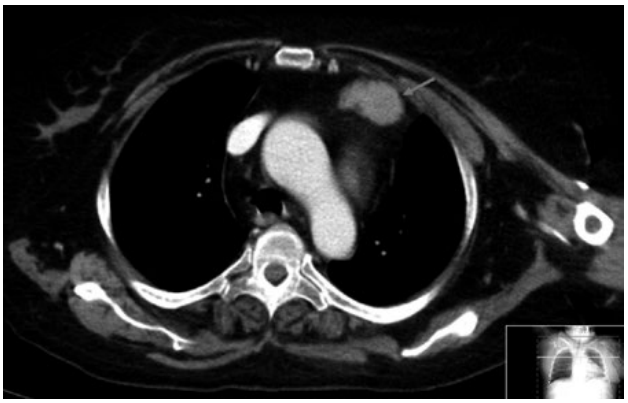
These ACTH-producing neuroendocrine tumours have a poor prognosis due to the usually exuberant Cushing syndrome that they cause, not exactly for the mass effect of the tumour itself, as was with this patient. When diagnosed in an advanced stage as such, the patient usually has several other illnesses and comorbidities that increase substantially the risk of severe complications and death. Also, the medical treatments available at that time could only delay the progression of the disease and its hormonal syndrome. The patient died of a sepsis secondary to pneumonia, probably aggravated by a weakened immune system due to ectopic Cushing syndrome. This case exemplifies how frequently secondary ectopic ACTH dependent Cushing syndrome's comorbidities, due to their aggressiveness, are the main cause for patients' morbidity and mortality. [1,9]

What is also particular in this case is the fact that the primary tumour was not visible in the initial imaging workup, leading the medical team to suppose that the cause was a small cell lung cancer.

Conclusion

Neuroendocrine tumours are rare and with poor prognosis. Due to their insidious presentation, many times with very small lesions responsible for hormonal syndromes, and its, sometimes, difficult location, a high level of suspicion and critical judgement is required to obtain a diagnosis. Treat-

Figure 2. CT Scan of Mediastinal mass (arrow)



ment remains incapable of achieving a cure in most of the patients with advanced disease, but can prolong life expectancy and manage hormonal complications as was seen in this patient.

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All Authors contribute equally to paper writing.

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