ACTH-secreting neuroendocrine pancreatic tumor: a case report.

ACTH-secreting neuroendocrine pancreatic tumor: A case report

Alessandra Surace, Alessia Ferrarese, Rosa Benvenga, Silvia Marola,
Jacopo Cumbo, Matteo Rivelli, Valter Martino, Mario Solej, Mario Nano

ABSTRACT

Introduction

Incidence of neuroendocrine tumor (NET) is increased in the last thirty years from 1.1 to 5.2 cases per 100,000 people in the United States. They can originate from the pancreatic gland and for the majority of cases are not functioning (80%). A small percentage of functioning may produce adrenocorticotropic hormone (ACTH) and lead to ectopic ACTH Syndrome (EAS), responsible of Cushing-Syndrome.

Results

We present a case of a 30 year-old woman suffering from EAS due to a neoformation of the pancreatic tail of the maximum diameter of 4 cm. The lesion was resectable at preoperatory imaging. The patient was subjected to distal splenopancreasectomy. Histological examination showed a well-differentiated neuroendocrine carcinoma pT3N0. The postoperative course was regular. At two years of follow-up patient is almost completely asymptomatic for Cushing's but she has developed multiple liver metastases, for which she began chemotherapy.

Discussion

p-NET responsible for EAS is usually malignant and the radical treatment of excision of the lesion is not possible because they occur at the time of diagnosis with liver metastases or unresectable. Our patient had a mass at the time of diagnosis resectable but despite radical surgery, she has developed multiple liver metastases at two years and she was undergoing chemotherapy.

Conclusions

In agreement with previous literature we confirm the aggressive nature of pancreatic tumors secreting ACTH, despite radical surgery. Conversely, surgical treatment is effective on the resolution of clinical symptoms.

1. Introduction

Cushing's syndrome caused by ectopic production of adrenocorticotropic hormone (ACTH or corticotropin) or EAS (Ectopic ACTH Syndrome) is responsible for 10–20% of Cushing's syndrome cases in the west countries [1] and 3.6% of cases in Japan [2]. Small cell lung carcinoma is the first cause of EAS, it is responsible of approximately 50% of all the tumors; other causes are indolent tumors as bronchial and thymic tumors, thyroid medullary carcinoma and gastroenteropathic neuroendocrine tumors (GEP-NET).

A dramatic increase was reported in neuroendocrine tumors incidence from 1.1 to 5.2 cases per 100,000 people, age-adjusted to the US population between 1973 and 2004 [3].

Such increase presumably depends on a few factors, including a more precise NET classification, endoscopy diffusion for tumors screening and other more sensitive imaging techniques as echoendoscopy and computerized tomography (CT) [4]. Regarding pancreatic NETs (pNET), incidence is 0.32 cases per 100,000 people per year, lower than lung, ileum and rectum NETs incidence (respectively 1.35, 0.67, 0.86, per 100,000). However, autopsic incidence of pNETs is higher (1.5% per year): this means that a considerable group of these tumors is underdiagnosed [5].

PNETs are classified as functioning (F-) and non-functioning (NF-), depending on the presence or not of an accompanying hormonal syndrome. NF-pNETs represent the majority of pNETs (60–80%). Insulinoma and gastrinoma are the most frequent (respectively 17 and 15%) among functioning pNETs; glucagonoma (1%), VIPoma (2%) and somatostatinoma (<1%) are less common [6]. There also exist other tumors producing ectopic hormone such as ACTH (1.2%) [7]. These pNETs are generally malignant except for insulinoma. The European Neuroendocrine Tumor Society (ENETS) and the World Health Organization (WHO) have suggested a strategy for the diagnosis and treatment of NETs. WHO has suggested the classification of NEs according to criteria such as the presence of metastases, the Ki-67/MIB-1 index, the histological grade, the vascular invasion and the tumor size [8]. The WHO classification of NETs includes: 1) well-differentiated NETs (benign or with an undefined biological behavior), 2) well-differentiated neuroendocrine carcinomas 3) poorly-differentiated neuroendocrine carcinomas. ENETS classification places NETs in three groups: G1, G2, G3, also according to the Ki-67/MIB-1 index and number of nuclear mitosis, as well as the TNM classification of large intestine NETs [9] and [10]. The EAS deriving from an ACTH -secreting pNET is a particularly aggressive disease, where metastases are observed in the initial phases of the clinical progress, even before the development of Cushing's syndrome clinical symptoms [11]. In patients with this type of pNET the two-year survival rate was 40% and the five-year survival rate was 16% [12]. Indications for surgical therapy in presence of pNET are to relieve symptoms caused by hormonal excess in patients with functioning tumors and to alleviate obstructive and constitutional symptoms in patients with non-functioning tumors.

Even though enucleation and distal pancreatectomy are the appropriate surgical options in many cases, pancreatoduodenectomy could be necessary in larger size tumors or in tumors that involve the periampullary region [13].

In this study, we report the case of a female patient who developed EAS due to a pNET.

1.1. Case report

We present the case of a 30 year old female patient, recovered in our ward after recovery in a medical area for suspect Cushing's syndrome due to ectopic production of ACTH.

The patient had been suffering from asthenia, face hypertrichosis and declive edemas for three months. The anamnesis reported a hospitalization for bleeding duodenal ulcer. A Cushingoid phenotype is described at entrance, showing BMI 27.4, moon facies, face hypertrichosis, striae rubra on the abdomen, arterial hypertension (160/100 mm Hg). Having suspected hypercholesterolemia, ACTH was dosed (79.5 pg/ml).

Upper abdomen CT was performed on patient and multiple hypodense formations, showing margins of the anterior surface of pancreas tail clear and partially confluent, were identified between the greater curvature of the stomach and the medial part of the spleen. Total body and segmentary scintigraphy using labeled Octreotide identified a weak extraphysiologic accumulation of the indicator in correspondence to the lesion shown by the CT. Abdomen echography confirms the presence of pancreas lesion, in absence of hepatic metastases. The patient completed the diagnostic procedure with hypophysis NMR with contrast medium (standard) and abdomen NMR, the latter describes thickening of the pancreatic tail due to a solid neoformation of 4 cm maximum diameter, indivisible from multiple formations of cystic aspect with thickened walls. The maximum global diameter of the wound is 10 cm.

The patient was therefore subjected to an operation of distal laparotomic splenopancreasectomy. Surgical picture does not highlight hepatic lesions, nor signs of peritoneal carcinosis. Neoproducing lesion, that is removed, is exhibited at pancreas level. The surgical specimen includes the tail of the pancreas measuring 8×5×3cm in association with a cystic formation of 10×4×4cm adjacent to the spleen of 4×8cm and of 150g. At pancreatic parenchyma level adjacent to cystic formation it is a yellowish neoformation of 4.5cm maximum of diameter that is distant 5cm from the pancreatic resection edge and that appears contiguous to the spleenic parenchyma without macroscopic evidence of direct invasion. Histological examination identified in pancreatic parenchyma a well-differentiated neuroendocrine carcinoma, with cystic component and focal extension to peripancreatic adipose tissue; mitosis 6/10 HPF, necrosis absent; extended angioinvasion; Ki67 23% (high proliferative index). The spleen appears congested, adherent but not infiltrated by neoplastic mass.

ENETS grading turned out to be G3, the stage pT3N0.

Neoplastic cell typing turned out to be pervasively positive to Chromogranin and focally positive to ACTH.

The patient was discharged on the 11th post-operative day. Upon discharge the patient is asymptomatic, in an euthymic mood.

After operation the patient hasn't undergone any adjuvant therapy. After two years in absence of symptoms, we attended Cushing's syndrome relapse with abdomen algia, asthenia and face hypertrichosis.

Abdominal TC shows: 7 hepatic lesions with a maximum diameter of 7.5 cm, most likely of a secondary nature. She underwent multiple TACE, which resulted ineffective.

On March 2013 she started chemotherapy with Capecitabine and Temozolamide.

2. Discussion

pNETs rarely produce ACTH with Cushing's syndrome symptoms. pNETs that determine EAS represent less than 1.2% of all pNETs in the Japanese population [4] and around 3.6% of all causes of EAS [2]. EAS-pNETs are usually malignant and they often present themselves with hepatic metastases at the time of diagnosis [8]. Because of the rapid disease progression, EAS-pNETs prognosis is low.

Usually pNETs affect more frequently female gender and localize in the head and body of the pancreas.

On average they measure 4.6 cm (2.5–7) [14].

In many cases the source of ectopic secretion of ACTH remains hidden for several years, in spite of multiple attempts of tumor localization. Signs and symptoms include increase in weight, central obesity, asthenia, glucose intolerance and hypertension. All patients have high levels of plasmatic and urinary cortisol [15],[16],[17]and[18]. Optimal treatment consists in localization and surgical exeresis of the tumor. Unfortunately, pancreatic ACTH-secerning tumors often appear with non-resectable hepatic metastases. Bilateral suprarenalectomy is often used with palliative intent to control symptoms of these patients [19].

The patient presented in the clinical case, even though not showing hepatic metastases during diagnosis, developed secondariness two years after surgical operation. Actual guide lines suggest chemotherapy as standard for metastatic NETs [9], although underlining that CT has a weak impact on patient survival rate, even if it obtains a good control of disease.

3. Conclusion

According to literature in our case we noticed a remission of endocrine symptoms after exeresis of tumoral mass. pNETs emerge as tumors characterized by marked biological aggressiveness. In our experience the disease represented itself with ACTH-secerning hepatic secondariness two years after diagnosis and after operation on primitive neoplasia.

Funding
All Authors have no source of funding.

Ethical approval
This is a retrospective study based only on the analyses of recorded data and then no Ethical Approval was necessary.

Author contribution

Alessandra Surace: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Alessia Ferrarese: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Rosa Benvenga: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Silvia Marola: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Jacopo Cumbo: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Matteo Rivelli: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data; also participated substantially in the drafting and editing of the manuscript.

Valter Martino: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Mario Solej: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Mario Nano: Participated substantially in conception, design, and execution of the study and in the analysis and interpretation of data.

Conflicts of interest

All Authors have no conflict of interests.

References

[**1**] B.L. Wajchenberg, B.B. Mendonca, B. Liberman, et al., Ectopic adrenocorticotropic hormone syndrome, Endocr. Rev., 15 (1994), pp. 752–787

[**2**] H.M. Nakagawa, K. Nawata, H. Takayanagi, et al., Nationwide Epidemiological Survey of Disorders of Adrenal Hormone Syndrome in Japan: a Survey for Rare Diseases, (1999)

[**3**] J.C. Yao, M. Hassan, A. Phan, et al., One hundred years after “carcinoid”: epidemiology and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States, J. Clin. Oncol., 26 (2008), pp. 3063–3072

[**4**] G. Rindi, C. Bordi, S. La Rosa, et al., Gastropancreatic (neuro)endocrine neoplasm: the histology report, Dig. Liver Dis., 43 (Suppl. 4) (2008), pp. S356–S360

[**5**] W. Kimura, A. Kuroda, Y. Morioka, Clinical pathology of endocrine tumors of the pancreas. Analysis of autopsy cases, Dig. Dis. Sci., 36 (1991), pp. 933–942

[**6**] I.M. Modlin, M. Zikusiva, M. Kidd, et al., The history and the epidemiology of neuroendocrine tumors, M. Caplin, L. Kvols (Eds.), Handbook of Neuroendocrine Tumors, Bioscientifica (2006)

[**7**] T. Ito, M. Tanaka, H. Sasano, et al., Preliminary results of a Japanese nationwide survey of neuroendocrine gastrointestinal tumors, J. Gastroenterol., 42 (2007), pp. 497–500

[**8**] G. Kloppel, Tumour biology and histopathology of neuroendocrine tumours, Best Pract. Res. Clin. Endocrinol. Metab., 21 (2007), pp. 15–31

[**9**] G. Kloppel, A. Couvelard, A. Perren, et al., ENETS guidelines for the standards of care in patients with neuroendocrine tumors: towards a standardized approach to the diagnosis of gastroenteropancreatic neuroendocrine tumors and their prognostic stratification, Neuroendocrinology, 90 (2009), pp. 162–166

[**10**] G. Rindi, G. Kloppel, H. Alhman, et al., TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system, Virchows Arch., 449 (2006), pp. 395–401

[**11**] J.L. Doppman, L.K. Nieman, G.B. Cutler Jr., et al., Adrenocorticotropic hormone — secreting islet cell tumors: are they always malignant?, Radiology, 190 (1994), pp. 59–64

[**12**] E.S. Clark, J.A. Carney, Pancreatic islet cell tumor associated with Cushing's syndrome, Am. J. Surg. Pathol., 8 (1984), pp. 917–924

[**13**] Gmo Q. Phan, Charles J. Yeo, et al., Surgical experience with pancreatic and peripancreatic neuroendocrine tumors: review of 125 patients, J. Gastrointest. Surg., 2 (1998), pp. 473–482

[**14**] K. Amikura, H.R. Alexander, J.A. Norton, et al., Role of Surgery in Management of Adrenocorticotropic Hormone-producing Islet Cell Tumors of the Pancreas, (1995 April 23–25) Presented at the Sixteenth Annual Meeting of the American Association of Endocrine Surgeons, Philadelphia, PA

[**15**] K. Amikura, H.R. Alexander, J.A. Norton, et al., Role of surgery in management of adrenocorticotropic hormone-producingislet cell tumors of the pancreas, Surgery, 118 (1995), pp. 1125–1130

[**16**] A. Dicitore, M. Caraglia, G. Gaudenzi, G. Manfredi, et al., Type I interferon-mediated pathway interacts with peroxisome proliferator activated receptor-γ (PPAR-γ): at the cross-road of pancreatic cancer cell proliferation, Biochim. Biophys. Acta., 1845 (1) (2014 Jan), pp. 42–52

[**17**] P. De Rai, A. Zerbi, L. Castoldi, C. Bassi, L. Frulloni, G. Uomo, A. Gabbrielli, R. Pezzilli, G. Cavallini, V. Di Carlo, ProInf-AISP (Progetto Informatizzato Pancreatite Acuta, Associazione Italiana per lo Studio del Pancreas [Computerized Project on Acute Pancreatitis, Italian Association for the Study of the Pancreas]) Study Group, Surgical management of acute pancreatitis in Italy: lessons from a prospective multicentre study, HPB Oxf., 12 (9) (2010 Nov), pp. 597–604

[**18**] R.K. Jex, J.A. van Heerden, P.C. Carpenter, et al., Ectopic ACTH syndrome: diagnostic and therapeutic aspects, Am. J. Surg., 149 (1985), pp. 276–282

[**19**] M.A. Zeiger, H.I. Pass, J.D. Doppman, et al., Surgical strategy in the management of non-small ectopic adrenocorticotropic hormone syndrome, Surgery, 112 (1992), pp. 994–1000