

An acute and severe immunodeficiency syndrome due to a pancreatic ACTH-producing tumor

Monica Cevenini, Elena Guidetti, Giulia Cacciari, Eugenio Ruggeri, Davide Campana, Paola Tomassetti, Roberto Corinaldesi

Dipartimento di Medicina Clinica. Università degli Studi di Bologna, Policlinico S. Orsola Malpighi, Bologna, Italia

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Abstract

We report a case of a 48 years old woman, with a rapidly progressing ACTH neuroendocrine tumor of the pancreas (PNET) and multiple liver metastases. The patient had previously suffered from peptic ulcer responsive to PPI inhibitors and hypertension poorly controlled by therapy. Admitted to the hospital for severe asthenia and abdominal pain, she was diagnosed poorly differentiated PNET with liver metastases, which were positive for synaptophysin, cytokeratin 7 and 9, neuron specific enolase (NSE). Octreoscan scintigraphy was positive for somatostatin receptor in the pancreatic and in two liver lesions. A rapidly progressive Cushing syndrome developed, presenting with the classical physical symptoms, hypokalemia and *Listeria Monocytogenes* meningitis. An ectopic ACTH production was confirmed and eventually the patient died of a septic shock within two months. The case reported focuses on the malignancy and the rapid progression of a PNET producing ACTH and alerts on the possible fatal progression of these cases.

Introduction

Ectopic ACTH secreting tumors account for 20% of Cushing's syndrome in Western countries and they are characterized by acute onset of hypercortisolism, signs of mineralocorticoid excess, weight loss, hyperpigmentation and immunodepression; they usually present with rapid progression of the disease (1-8).

About 50% of all ectopic ACTH secreting tumors is given by small cell lung carcinoma, the remaining are represented by other tumors, such as pancreatic, bronchial, thymic tumors and thyroid medullary carcinoma or pheochromocytoma. In a 8-19% of cases the primary tumor remains undetected (9-11). We report a fatal case of an acute Cushing's syndrome associated with immunodeficiency in a patient with an advanced pancreatic tumor metastatic to the liver at the onset of the syndrome.

Case report

A 48-year old woman was admitted to the hospital in August 2011 presenting with severe asthenia, abdominal bloating and weight gain for over a month. Her recent clinical history included a poorly-responsive blood hypertension and endoscopically proven gastric ulcer treated with standard doses of proton pump inhibitors (omeprazole 20 mg/die). Blood analysis showed severe anemia (Hb 9.8 g/dl), reduced hematocrit (Ht 31.9%), neutrophilic leukocytosis with marked lymphocytopenia ($10.66 \times 10^3/\text{ul}$; lymphocytes: $0.52 \times 10^3/\text{ul}$), hypertransaminasemia (AST 56U/L; ALT 89U/L). At the time of that admission, the patient did not show any clinical features of Cushing's syndrome. Furthermore, because of the clinical picture, the patient underwent a thorough endoscopic examination, with esophagogastroduodenoscopy and colonoscopy which ruled out a gastrointestinal bleeding. The abdominal ultrasound examination showed a mass located in the head of the pancreas along with multiple liver metastases, a finding confirmed by the CT-scan. The lung was apparently spared of any metastatic lesion. A liver biopsy showed a high grade, poorly differentiated neuroendocrine carcinoma (grade G3, Ki67 of 55.9%) At histopathology, tumor cells showed a diffuse cytoplasmic positivity for a number of neuroendocrine markers, including neuron specific enolase (NSE), synaptophysin, chromogranin A (CgA) and cytocheratin-7 and -9 (Fig. 1, 2).

Serum NSE and CgA were elevated (235 ng/ml, n.v. <12.5 ng/ml and 354 ng/ml, n.v. <35 ng/ml, respectively).

The octreoscan scintigraphy revealed a mild accumulation in the head of the pancreas in a location compatible to that identified by CT-scan and ultrasonography. Furthermore, octreoscan evaluation indicated a radionuclide accumulation in only two lesions of the liver. These findings clearly indicated a neuroendocrine origin of the pancreatic tumor and related metastases. Three months later the patient was again hospitalized for acute sepsis due to *Listeria Monocytogenes* meningitis and *Staphylococcus Aureus* metycillino-resistant multiple broncho pneumonitis. In addition, the patient showed a severe leukopenia, marked glucose intolerance and severe hypokalemia unresponsive to replacement treatment. Shortly after, the patient developed jaundice, rounded plethoric face, buffalo hump, hyperpigmented abdominal cutaneous striae, hirsutism and muscle weakness: all signs clearly indicative of Cushing's syndrome. Serum tests resulted as follows: ACTH 338 pg/ml (n.v.:

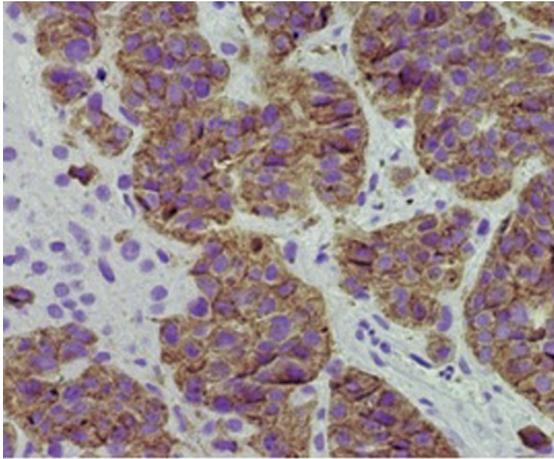


Fig. 1. Synaptophysin Hematoxylin eosin.

secreting tumor accounting for 1.2% of all PNETs and 15% of ectopic ACTH syndrome. ACTH-secreting tumors occur most frequently in adults, mainly females as the case herein illustrated. Most tumors appear to have a well-differentiated histopathological phenotype, while rare cases show a poorly-differentiated neuroendocrine profile (15-17). In this case report, we provided evidence of a female patient with a particularly aggressive form of poorly-differentiated pancreatic ACTH producing tumor. In the few cases so far published, this type of rare PNET usually presents with an aggressive behavior often characterized by metastasis at the time of diagnosis. In addition to liver, common sites of secondary location of the primitive tumor include lymph nodes, kidneys, bone, thyroid and peritoneum. Previously, a case with ovarian metastasis has been described (18). Due to the rapid progression of disease, the prognosis is poor and the survival rates were 40% and 16% at 2 and 5 years, respectively (19). The course of the tumor-related Cushing's syndrome can be either acute (usually rapidly progressive) or chronic. The acute presentation, as apparently occurred in our patient, is associated with a rapid onset of hypertension, edema, hypokalemia, diabetes, but without the typical Cushing features. This clinical phenotype is generally due to an underlying small cell lung carcinoma (20-23). In contrast, the chronic presentation of an ectopic ACTH secreting tumor is as-

5-60 pg/ml); cortisol > 630 ng/ml (n.v.: 62-194 ng/ml), and free urinary cortisol > 630 mg/die (n.v.: 36-137 mg/die). A further immunohistochemical evaluation of the liver metastases confirmed the presence of ACTH containing cells (Fig. 2). Thus, taken together the clinical outcome, endocrinological laboratory assays and newly performed immunohistochemical analysis of available tissue were all consistent with an ectopic ACTH secretion by a neuroendocrine pancreatic tumor. The outcome of the disease was characterized by a rapid evolution leading the patient to death for acute septicemia unresponsive to any antibiotic treatment.

Discussion

Pancreatic neuroendocrine tumors (PNETs) are rare neoplasms, accounting for less than 3% of all pancreatic tumors and 5-7% of all neuroendocrine tumors (NETs) (12). Functioning tumors represent only 10% of PNETs (13) and they may produce peptide hormones, such as insulin, glucagon, somatostatin and pancreatic polypeptide. PNETs are generally malignant except insulinoma (13,14). In this context, an even rare neoplasm is represented by pancreatic ACTH

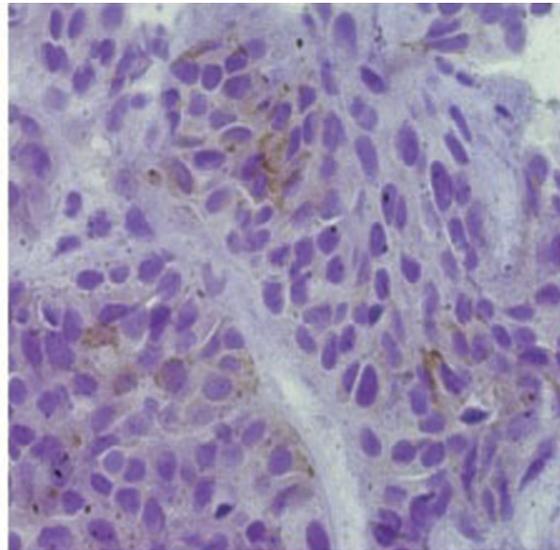
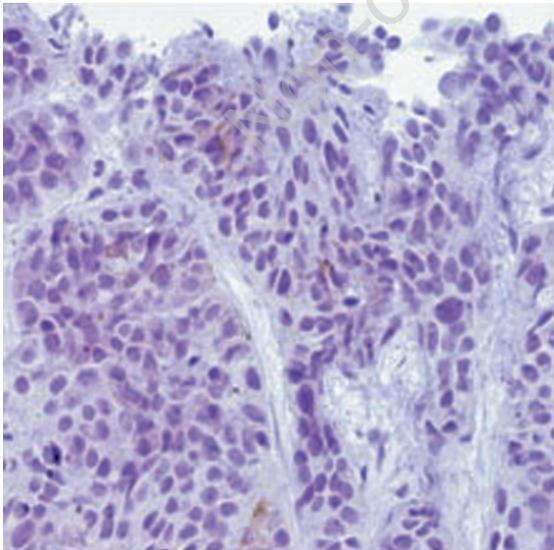


Fig. 2. Liver biopsy: Synaptophysin and Hematoxylineosin – immunostaining.

sociated with the typical Cushing's syndrome. The case herein reported is atypical as the patient showed clinical signs indicative of both acute and chronic presentation of the tumor. Indeed, our patient had clinical manifestations suggestive of a chronic presentation (i.e., Cushing's Syndrome) rapidly complicated with a cohort of other symptoms and signs related to hypercortisolemia, including severe immunodeficiency. These features along with a number of tests led to establish a diagnosis of an ectopic ACTH secreting tumor. However, one cannot rule out the possibility that our patient had a sub-clinical Cushing syndrome preceding the overt manifestations leading to referral in our Neuroendocrine Tumor Unit.

A peculiar feature of ectopic ACTH secreting tumors, in particular those with features of a pancreatic mass, is the phenotypic behavior characterized by tumor cells changing from a non-secreting to an ACTH secreting functional profile. This changing (non-secreting to secreting) profile may be related to a loss of cell differentiation by the tumor over time (14). In our case, whether an ectopic ACTH production was due to the original pancreatic lesion or the liver metastases remained unsettled. The short time from the identification of liver metastases and Cushing's syndrome made us unable to establish a certain origin of ACTH production. The malignant potential of the tumor, as observed in this case, is further supported by the evidence that most of the metastatic lesions turned to be negative at the somatostatin receptor scintigraphy, suggesting their loss of cell differentiation.

In our patient we were able to obtain tissue only from liver biopsy which proved a positive ACTH-containing cells conceivably related to the original pancreatic tumor. As previously reported, the ACTH immunoreactive component is mixed with a sub-population of non-secreting cells, which is a common finding in this type of PNETs (24).

A further feature of this case was the severe cortisol-dependent immunosuppression, which was a critical factor leading to the rapidly patient death. To our knowledge, this is feasible and clearly supported by the cortisol effect on the immune system, however the severity and rapid progression due to the occurrence of a septicemia is quite uncommon.

In our patient, we could not attempt any surgical or medical treatment. Wherever possible the gold standard treatment include surgical resection of the primary ectopic ACTH-secreting tumor or, as an alternative, bilateral adrenalectomy may be indicated in order to control cortisol secretion. The medical therapy is based on drugs inhibiting the synthesis and secretion of cortisol, such as ketoconazole, metyrapone and mitotane (25-26). Usually, ketoconazole and metyrapone are effective, although often limited by the lack of control of hypercortisolism related to unsuppressed ACTH secretion (27). In this line, our patient had such a rapid evolution of the clinical picture hampering any possible treatment with somatostatin analogues or other novel cytostatic agents, e.g. everolimus now indicated in patients with advanced PNETs (28).

In conclusion, this case reported appears of special interest for internists and specialists alike as it showed a rapid progression of an atypical Cushing's syndrome related to an ACTH secreting PNET. The present clinical report highlights the aggressive nature of this tumor and alerts on the rapidly fatal course of this condition.

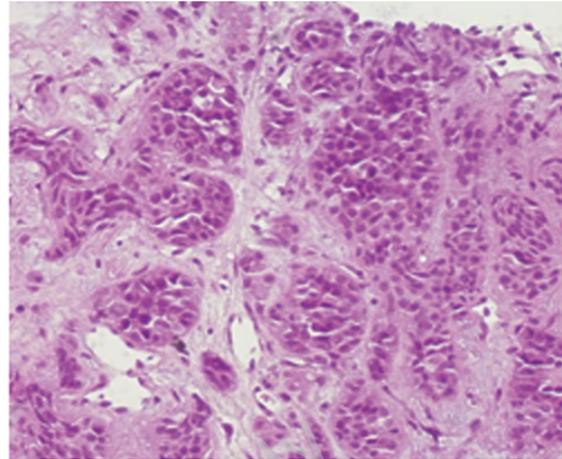


Fig. 3. Liver biopsy: ACTH-immunostaining.

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