

## Case Report

# ACTH-secreting pancreatic neuroendocrine carcinoma with ovarian and pelvic metastases causing Cushing's syndrome: a case report

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**Abstract:** Adrenocorticotropin hormone (ACTH)-secreting pancreatic neuroendocrine carcinoma (NEC) with ovarian and pelvic metastases causing Cushing's syndrome is very rare and might be misdiagnosed. We describe a case of ACTH-secreting pancreatic poorly differentiated NEC developing bilateral ovarian and pelvic metastases. A 27-year-old woman presented with thirst, polydipsia, fatigue and poorly controlled hyperglycemia. Laboratory and imaging investigations revealed hypokalemia, hyperglycaemia, ACTH-dependent hypercortisolemia and a 12-cm mass at the junction of body and tail of the pancreas with ovarian and pelvic nodules. The patient underwent partial pancreatectomy and splenectomy, uterectomy, bilateral oophorectomy, and excision of peritoneal nodules. Tumors in pancreas, ovaries and pelvis were diagnosed as poor-differentiated NEC. After 19-month chemotherapy, she developed pelvic metastasis. The tumor in our case is a large, poorly differentiated NEC secreting ACTH and causing CS, with ovarian metastases. To our knowledge, this new additional case of ACTH-secreting pancreatic NEC with ovarian metastases would add to the better understanding of this tumor.

**Keywords:** ACTH, pancreatic neuroendocrine neoplasms, ovarian metastasis

## Introduction

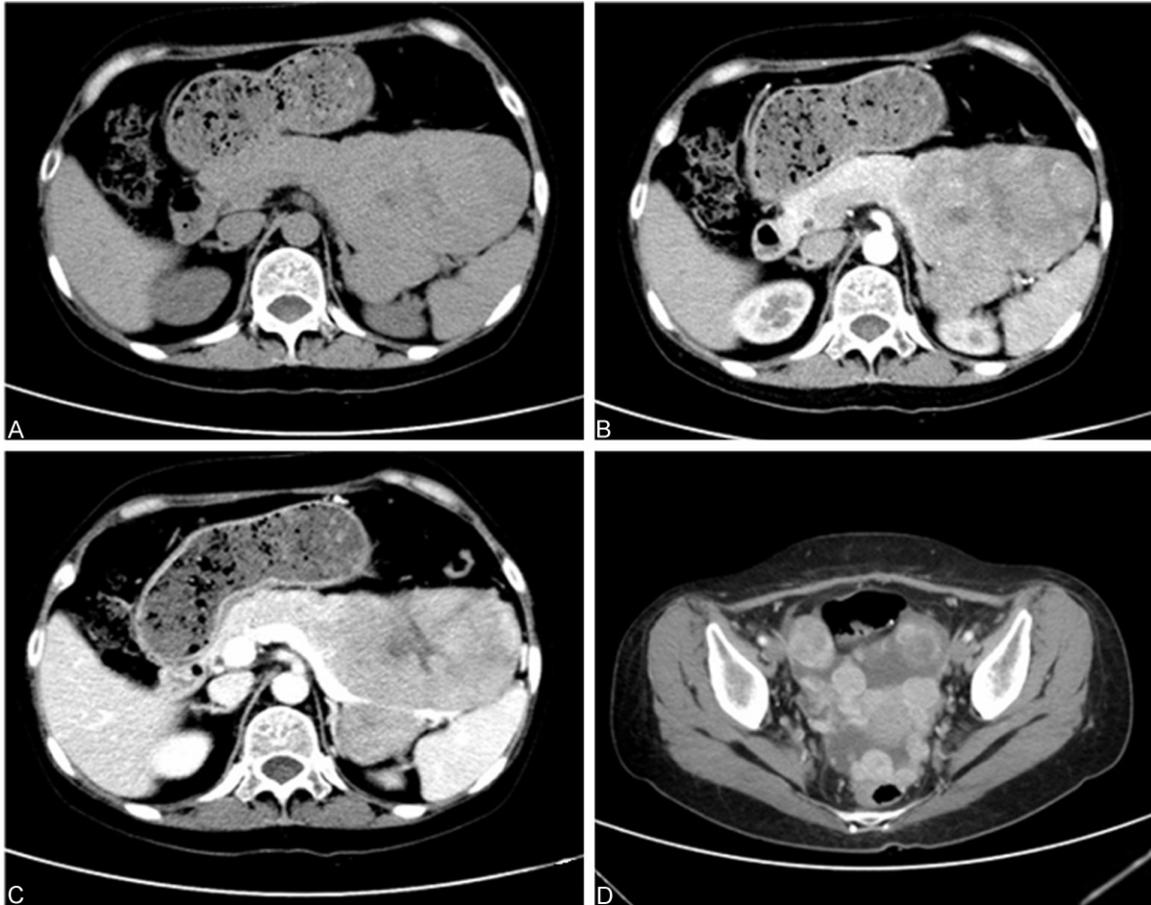
Pancreatic neuroendocrine neoplasms (P-NENs), once called islet cell tumor, APUDoma, are uncommon neoplasms, and account for 1%-2% of all pancreatic neoplasms [1]. P-NENs associated with characteristic clinical syndromes due to the hypersecretion of hormones are called functioning P-NENs [1, 2], accounting for 60%-70% of all P-NEN based on surgical series; others are called nonfunctional P-NENs [1, 3]. P-NENs secreting adrenocorticotropin hormone (ACTH) and causing Cushing's syndrome (CS) are quite rare, and account for 4%-16% of ectopic CS. It is extremely rare for pancreatic neoplasms, either endocrine or exocrine, to develop ovarian and pelvic metastases without liver metastasis. Here, we present the clinical, light microscopic, immunohistochemical and electronic microscopic findings on a rare ACTH-secreting pancreatic neuroendocrine carcinoma (NEC) causing CS with ovarian and pelvic metastases.

## Case report

### *Clinical manifestation*

A 27-year-old female went to the local hospital complaining of thirst, polydipsia, nocturia and fatigue. After taking a fasting blood-glucose test with a result of 7.8 mmol/L, she was diagnosed with diabetes mellitus and recommended oral diformin tablets. However, her blood sugar remained above the normal level. She was then prescribed subcutaneous insulin injection, but her postprandial blood glucose level still remained over 15 mmol/L. Four months later, the patient developed somnolence, dull reaction, blurring vision and menopause, which brought her to an obstetrics and gynecology hospital. There, she underwent transvaginal ultrasonography, which revealed masses located in the bilateral ovaries and pelvic peritoneum, and surgery was recommended.

Physical examination showed that the patient had facial erythema, bruises, purple striae and



**Figure 1.** CT images of the tumor at diagnosis. A-C showed CT images of the pancreatic mass. A was plain scan, B and C were contrast-enhanced images obtained in arterial phase and portal venous phase, respectively. The pancreatic mass located at the junction of the pancreatic body and tail was well-circumscribed, manifested heterogeneous enhancement in arterial and portal phase images. C illustrated the splenic vein wrapped around by the pancreatic mass. D was images of the pelvic masses of arterial phase. The masses were well-limited, heterogeneous enhancement in arterial phase image.

hirsutism. Laboratory testing revealed hypokalemia, hyperglycemia, high plasma ACTH, high serum cortisol, elevated 24-hour urinary free cortisol excretion, with no response to low-dose or high-dose dexamethasone suppression tests. The patient's cephalic CT was normal, while abdominal CT scans showed a well-circumscribed mass located at the junction of the pancreatic body and tail along with several well-delimited nodules in the pelvic cavity. The pancreatic mass was wrapped around the splenic vein and approximately 12 cm×11 cm×9 cm in size. The mass had a low density area inside indicating necrosis, and manifested heterogeneous enhancement in arterial and portal phase images. The pelvic nodules were attached to the ovaries, uterus, rectouterine pouch and mesentery, with enhancement in arterial phase images (**Figure 1**). The adrenal glands showed no signs of enlargement.

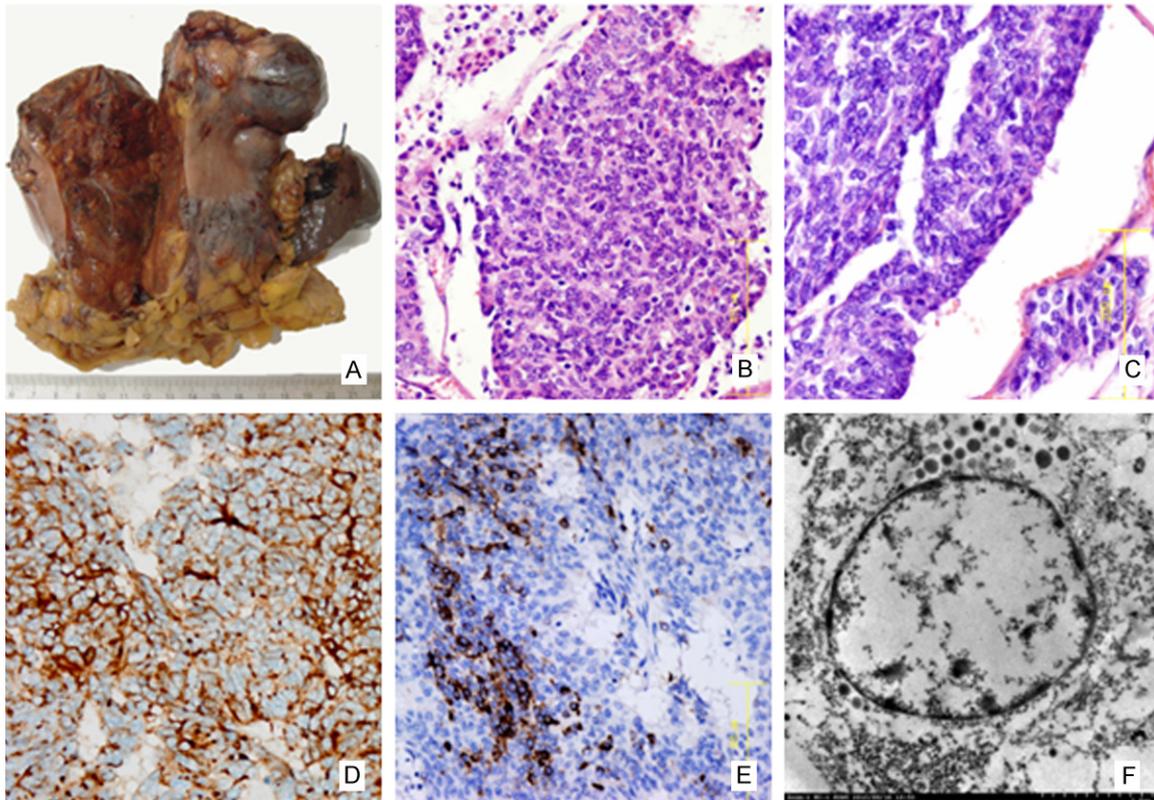
The patient underwent partial pancreatectomy, splenectomy, uterectomy, bilateral oophorectomy, and excision of peritoneal masses.

#### *Histology, immunohistochemistry and electron microscopy*

The biopsy specimen was fixed in 10% formalin solution and embedded in paraffin blocks. Sections were cut and stained with hematoxylin and eosin (HE) for microscopy. Immunohistochemical (IHC) studies were performed using the 2 step Envision procedure and a DAKO Autostainer (Dakopatts, Copenhagen, Denmark).

For the ultrastructural examination, samples were retrieved from formalin-fixed tissue and then immersed for 2 h in a mixture of 2% paraformaldehyde and 2% glutaraldehyde in 0.05 M pH 7.3 cacodylate buffer. The samples were

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**Figure 2.** Pathological images of the tumor. A demonstrated the gross image of the pancreatic mass and spleen. The cut surface of the tumor was solitary, white-yellow, soft and fleshy. B to E illustrated HE and IHC stain of the tumor, with the magnification of 400. B and C were tumor of the pancreas and ovary, separately. Histologically, the tumors exhibited similar features, and displayed diffuse, irregular sheets of cells with scattered necrosis. D and E showed chromogranin A and ACTH staining of the pancreatic mass, which were cytoplasmic positive. F was electron micrograph of a tumor cell. There were numerous round secretory granules with an electron-dense core in the cytoplasm with the diameter of 100-300 nanometer.

post-fixed in 1% osmium tetroxide for 1 h at room temperature, dehydrated in ethanol, and then embedded in Epon-Araldite. Thin sections were counterstained with uranyl acetate and lead citrate and examined using a Hitachi (H-7650) electron microscope.

### Macroscopy

The pancreatic mass was 12 cm×12 cm×8 cm, well-demarcated, solitary, white-yellow, soft and fleshy (**Figure 2A**). The uterus was of normal size with several nodules attached to the left fallopian tube and the bilateral ovaries were enlarged with smooth nodules on them. The cut surfaces of the masses located in ovaries, fallopian tube and peritoneum were similar to the cut surface of the pancreatic mass.

### Histology

Histologically, the pancreatic and pelvic masses exhibited similar features. They displayed

diffuse, irregular sheets of cells with scattered necrosis. The tumor cells were round to polygonal with scarce cytoplasm and vesicular nuclei (**Figure 2B, 2C**), and the mitotic figure was 211 in 100 high power fields. No lymph node metastasis was found.

IHC staining of the pancreatic tumor showed that the tumors were positive for cytokeratin, epithelial membrane antigen, synaptophysin, chromogranin A (**Figure 2D**) and ACTH and negative for insulin, somatostatin, gastrin, glucagon, CD10,  $\alpha$ -1-antitrypsin, trypsin, and  $\alpha$ -chymotrypsin. The Ki-67 index was 25%. ACTH staining of the pelvic mass was scarcer than in the pancreatic mass (**Figure 2E**).

Electron microscopic examination revealed numerous round secretory granules with an electron-dense core and a narrow electron-lucent halo in the cytoplasm of the tumor cells (**Figure 2F**).

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### *Pathological diagnosis*

The pathological diagnosis was pancreatic NEC, G3, with metastases of the ovaries and mesentery. The World Health Organization (WHO) stage grouping was T2NOM1, stage IV according to the 2010 WHO classification of tumors of the digestive system [1].

### *Therapy and prognosis*

The patient's cortisol and ACTH levels returned to normal a week after the operation. Afterward she underwent 7 cycles of chemotherapy (consisting of the intravenous administration of platinum diamminodichloride at 30 mg/day for 3 days and VePesid at 100 mg/day for 4 days). Her Cushingoid features fully subsided, and a CT scan showed no signs of metastases. However, 19 months after the surgery an enlarged lymph node near the right iliac vessel was detected by CT scan and was thought to be a metastasis. The patient underwent a modified chemotherapy regimen in which the platinum diamminodichloride was increased to 40 mg/day on the 2<sup>nd</sup> and 3<sup>rd</sup> day of chemotherapy. However, another CT scan revealed that the lymph node was larger after 2 cycles. The patient refused further chemotherapy and was lost to follow-up.

### **Discussion**

ACTH-secreting P-NENs associated with CS are responsible for approximately 4%-16% of ectopic CS [2, 4-6]. Our case was initially misdiagnosed as diabetes mellitus based on her hyperglycemia without taking her other symptoms (facial erythema, bruises, purple striae and hirsutism) and laboratory test results (hypokalemia, high plasma ACTH, high serum cortisol) into account. Clinicians should be aware of this rare possibility in young patients with hyperglycemia exhibiting no or a poor response to oral antidiabetic agents and insulin injection.

In our case, the pancreatic tumor located at the junction of the pancreatic body and tail had a diameter of 12 cm when diagnosed, larger than most other ACTH-secreting P-NENs reported in the literature [7-14]. This size may be attributable to the following two reasons. First, neoplasms of the pancreatic body and tail, unlike neoplasms of the head of the pancreas which usually develop obstruction of the distal com-

mon bile duct and cause jaundice, do not impinge on the biliary tract and hence can remain silent for some time. By the time they are discovered, the neoplasms of the body and tail may be quite large and widely disseminated, developing local invasion and peritoneal metastases. Second, ACTH secreted by pancreatic neoplasms is decomposed in the liver through enterohepatic circulation within several minutes [15]. Patients will not seek medical help unless the neoplasm is large enough to produce enough hormones to cause a clinical syndrome. In contrast, ACTH released by bronchial and thymic neuroendocrine neoplasms (NENs), which are smaller than 1 cm in diameter, enters the systemic circulation directly, leading to clinical CS within a short time [6].

ACTH is not produced by the pancreas, and thus ACTH-secreting P-NENs may suggest a primitive or embryonic transformation [1]. This origin might explain why the tumor in our case was morphologically poorly differentiated and graded G3 according to the 2010 WHO classification of tumors of the digestive system [16], which is quite different from previous cases [14]. In Maragliano's review of 134 cases of ACTH-secreting P-NENs causing CS, only 6% were morphologically poorly differentiated and were considered as NEC. The ACTH staining of the pancreatic tumor in our case was more prominent than in the ovarian masses, indicating that the latter were even more primitive.

Pancreatic neoplasms, either endocrine or exocrine, often extend through the retroperitoneal space, entrapping adjacent nerves and organs, and cause local lymph node metastases as well as distant metastases [17]. Up to 78.7% of ACTH-secreting P-NENs have exhibited distant metastases when diagnosed. The most common metastasis sites of ACTH-secreting P-NENs are the liver and lung, but other sites include the adrenal glands, bone, kidney and omentum.

Primary ovarian NENs account for 0.5%-1.7% of all NENs and are mostly unilateral [18]. Bilateral ovarian involvement of NEN usually suggests metastatic tumors [19], mostly from the intestine or lung [1, 18-20]. Ovarian metastatic NENs from the pancreas are rare. Only 2 cases have been previously reported [9, 21] and this study represents the third case of an ACTH-secreting pancreatic NEN with ovarian metas-

tases. Our case developed peritoneal implants and bilateral ovarian involvement, suggesting that the tumor spread through direct peritoneal seeding.

The adrenal glands in patients with adrenocorticotropin-dependent CS are characterized by variable degrees of bilateral nodular cortical hyperplasia, caused by elevated levels of ACTH. Eighty-two percent (110/134) of ACTH-secreting P-NEN patients with CS had been reported to have adrenal hyperplasia [14]. However, in our case, the CT scan showed no signs of cortical hyperplasia, similarly to one previously reported case of an ACTH-secreting P-NEN with ovarian metastasis [11]. We assume that the normal adrenal gland in our case, might result from the short time of the disease (6 months).

### Conclusions

We described a rare case of pancreatic ACTH-secreting NEC causing CS with pelvic and bilateral ovarian metastases. ACTH-secreting P-NENs may mimic diabetes mellitus and be misdiagnosed, thus calling for attention in clinical practice. The tumor could grow large, be poorly differentiated and of high grade and develop metastases to the ovaries. Our findings would add to the better understanding of ACTH-secreting pancreatic NEN.

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### Disclosure of conflict of interest

None.

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