

# Cushing Syndrome Caused by a Pancreatic Neuroendocrine Tumour and Its Pelvic Metastases

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## ABSTRACT

*Cushing's syndrome caused by an ectopic tumour secreting adrenocorticotrophic hormone (ACTH) is not common. Furthermore, an ACTH-secreting pancreatic neoplasm is extremely rare. We present a 27-year old female patient suffering from a pancreatic neuroendocrine tumour (p-NET) with extensive pelvic metastases, which could secrete ACTH and cause Cushing's syndrome. The postoperative pathologic examinations of this patient prompted pancreatic poorly differentiated neuroendocrine tumour with extensive metastases of bilateral ovarian, uterus and pelvic peritoneum. The immunohistochemical staining of her tumour tissues was positive for Chromogranin A, Synaptophysin and ACTH. The main aim of this article is to share the experience of her diagnosis and treatment and to review the relevant literature, with an emphasis on discussing the possible transfer modes. Moreover, we strongly suggest that a careful examination of pelvic cavity during the follow-up of patients diagnosed as ACTH-secreting p-NET should also be carried out.*

**Keywords:** Cushing's syndrome, ectopic ACTH secretion, pancreatic neuroendocrine tumour, pelvic cavity

# El síndrome de Cushing causado por un tumor neuroendocrino pancreático y sus metástasis pélvicas

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## RESUMEN

*El síndrome de Cushing causado por un tumor ectópico secretor de la hormona adrenocorticotrópica (HACT) no es común. Además, un neoplasma pancreático secretor de HACT es extremadamente raro. Presentamos una paciente de 27 años de edad con un tumor neuroendocrino pancreático (TNEP) con metástasis pélvicas extensas, que secretaba hormonas HACT y causaba el síndrome de Cushing. Los exámenes patológicos postoperatorios de esta paciente indicaron un tumor neuroendocrino pancreático pobremente diferenciado, con metástasis extensas de ovario bilateral, útero y peritoneo pélvico. La coloración inmunohistoquímica de los tejidos de su tumor fue positiva a la cromogranina A, la sinaptofisina y la HACT. El objetivo principal de este artículo es compartir la experiencia de su diagnóstico y tratamiento, así como la revisión de la literatura relevante, con énfasis en el examen de los modos de transferencia posible. Además, sugerimos enfáticamente que también debe llevarse a cabo un examen cuidadoso de la cavidad pélvica durante el seguimiento de los pacientes diagnosticados con TNEP secretor de HACT.*

**Palabras clave:** Secreción ectópica de HACT, síndrome de Cushing, cavidad pélvica, tumor neuroendocrino pancreático

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**INTRODUCTION**

Cushing’s syndrome (CS), which was first reported by Harvey Cushing in 1932 (1), refers to a series of typical clinical manifestations such as full moon face, buffalo back, skin pigmentation, hair increase, anasarca, high blood pressure, hypokalaemia and menopause, *etc.* Cushing’s syndrome is caused by an excess of high level of cortisol in the blood, which could be secreted by pituitary, adrenal and other neuroendocrine tissues (2). The symptoms caused by non-pituitary tumours, which can also secrete adrenocorticotropic hormone (ACTH) that is biologically and immunologically indistinguishable from that of the pituitary, are named Cushing’s syndrome secondary to an ectopic ACTH secretion [CS-EAS] (3). It has been reported to be about 8% to 18% of all causes of CS, which consisted of a wide variety of tumours, such as small cell lung cancer, bronchial carcinoid, thymoma, *etc* (4–6). Cushing’s syndrome caused by an ACTH-secreting pancreatic neuroendocrine tumour (p-NET) is not common (7), not to mention a tumour with extensive metastases in the pelvic cavity. To the best of our knowledge, only two cases have been reported till now (8–9). Here, we present another one from our centre, aimed at sharing the experience of the diagnosis and treatment and reviewing the relevant literature, with an emphasis on discussing the possible transfer modes of this rare clinical phenomenon.

**CASE REPORT**

A 27-year old female patient was admitted into the endocrinology service of our hospital with a main complaint of dry mouth, thick beard and menopause for over two months. After admission, her physical examinations showed typical CS: chronic ill face rough and dull skin with pigmentation, thick beard, oedema of both legs, full moon face and fat pads behind the neck. The blood tests of this patient showed an over secretion of cortisol and ACTH. Furthermore, her cortisol secretion was not suppressed with high-dose dexamethasone (Table).

The abdominal and pelvic multi-phase enhanced computed tomography (CT) scan detected a giant solid and cystic mass in the body and tail of the pancreas with a size of approximately 12 x 12 x 10 cm<sup>3</sup> and many round solid masses, about 1–3 cm in diameter, in the pelvic cavity (Fig 1: a–d).

This young patient was switched to the Department of Hepato-bilio-pancreatic Surgery of our hospital for surgical treatment after a joint consultation. Then, “the distal pancreatic resection” was successfully performed, in which we found the patient’s adrenals had no abnormality and that, the quick frozen pathology of the tissues taken from the ovary tumour had the same components as the body and tail of the pancreas. Therefore, two other operations, “total hysterectomy and bilateral oophorectomy resection”, were added after a timely consultation by the gynaecologist. Her postoperative pathologic diagnosis (Fig 2: e, f) revealed that the: Pancreatic body and tail had neuroendocrine carcinoma World Health Organization [(WHO) current classification: NET G2]. Pelvic masses bilateral and bilateral

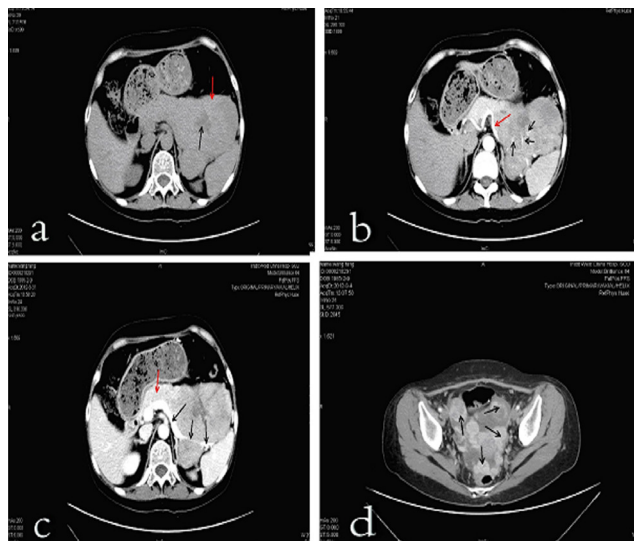


Fig 1: a (plain scan): A soft-tissue mass can be seen in the body and tail of the pancreas (red arrows), with internal low-density focal necrosis (black arrow). b (arterial phase): The mass, with an uneven strengthening and many internal visible small blood vessels (black arrows), has a close relationship with a splenic artery (red arrow). c (portal vein phase): Surrounding the splenic vein (black arrow), the tumour boundaries are clear with the normal pancreas tissue (red arrow). d: Many round enhanced masses can also be detected in the pelvic cavity (black arrows).

Table: The secretions of cortisol and adrenocorticotropic hormone in the blood and urine of our patients

	Blood cortisol (normal range: 147.3–609.3 nmol/L)	Blood ACTH (normal range: 5.0–78 ng/L)
8:00–10:00	> 1750 nmol/L	101.5 ng/L
16:00–18:00	1465.00 nmol/L	146.60 ng/L
24:00	1636.00 nmol/L	96.24 ng/L
Oral 8 mg dexamethasone	1508 nmol/L	78.01 ng/L
24-hour urinary free cortisol	2762.6 ug/24hr (normal range: 134.83–93.81 nmol/24hr)	

ACTH: adrenocorticotropic hormone

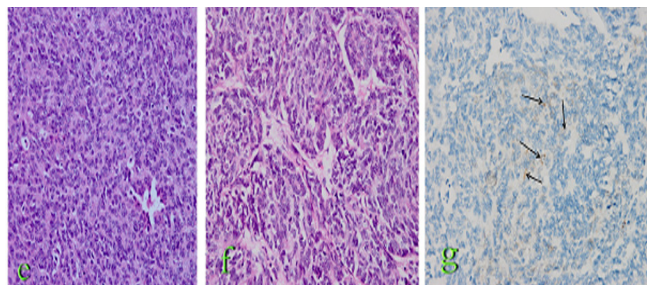


Fig 2: e, f: The proliferation of tumour cells has a diffuse distribution in the resected masses of both pancreas and ovary. g: Immunohistochemical staining of tumour tissue was positive for adrenocorticotropic hormone (black arrows).

ovarian nodules were both tumour-infiltrating/metastatic nodules. The staining of her tumour tissues was positive for chromogranin A, synaptophysin and ACTH in the immunohistochemical examinations (Fig 2g) and their Ki-67 positive rate was 8%.

## DISCUSSION

The ACTH-secreting p-NET, through very rare, has been reported before (7, 10–12), in which most of the tumours were composed of small to medium-sized masses and were partly reported to be malignant with metastases in lymph nodes, liver, kidney and bone, *etc* (13). However, the extensive pelvic metastases from a giant ACTH-secreting p-NET were extremely rare. Öberg *et al* (8) reported one case, whose tumour had a low aggressiveness and presented with ovarian metastases at the beginning of diagnosis. The patient recovered well after a successful surgery and was free of this disease for more than six years, postoperatively. The other one reported by La Rosa *et al* (9) did not have ovarian metastases at the time of first diagnosis. With an unresectable p-NET already associated with lymph node and liver metastases when diagnosed, this patient was endocrinologically well controlled for about seven years until ovarian metastases appeared. But she died soon after due to the worsening of her symptoms. Herein, together with the present case, we speculated the metastases in pelvic cavity might probably derive from the malignant ACTH-secreting tumour of the pancreas through planting transfer, for the pelvic cavity was a high-risk place of invasion by gastrointestinal and retroperitoneal malignant tumours. Therefore, we strongly and sincerely suggest that pelvic cavity should also be considered among the possible metastatic sites of ACTH-secreting the p-NET and that a careful examination of the pelvic cavity during the patients follow-up should be carried out in a timely way.

Associated with the clinical data and pathological analysis of our patient, the ACTH-secreting tumour of the pancreas could be classified into a poorly differentiated neuroendocrine tumour (NET G2) and T4N1M1 (Stage IV) according to the WHO (2010) classification (14) and the European TNM grading system (15), and mostly has a rather difficult treatment and poor prognosis. However, surgical resection still has been the golden standard in the treatment of p-NETs, both as radical tumour excision and palliative treatment aimed at alleviating the clinical complaints and improving the quality of the patient's life (16, 17). At follow-up two months after surgery, our patient had changed greatly because of the disappearance of her main manifestations and quality of life was good at 14 months after operation.

However, considering the biological behaviour and the origin of malignant tumours, as well as the complexity of operations, her subsequent quality of life and survival time are still worth follow-up.

## AUTHORS' NOTE

We declare that we have no conflict of interest among the authors and we don't have any sponsorship.

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