Case Report

Ectopic ACTH syndrome caused by thymic neuroendocrine tumor: a case report and literature review

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Abstract: A 36-year-old woman presented with onset of reduced menstrual flow, gradually progressed to typical Cushingoid features with 24-hour urine free cortisol (UFC) increased, low-dose dexamethasone suppression test and high-dose dexamethasone suppression test both not suppressed, adrenocorticotropic hormone (ACTH) increased, and computed tomography (CT) scan of the chest revealed a large mass in the anterior mediastinum. The local hospital administered mediastinal mass resection which afterwards showed type B1 thymoma. The above symptoms were relieved post-operation, and the levels of ACTH and cortisol decreased. Symptoms recurred 5 months after the surgery, with laboratory and imaging suggested possible multiple tumor metastases. The patient was referred to our hospital and was diagnosed with ectopic ACTH syndrome and thymic neuroendocrine tumor with multiple metastases post-operation. After administered mifepristone to antagonize the glucocorticoid receptor, the patient's symptoms improved. The patient also received "etoposide" single-agent chemotherapy, and the symptoms were relieved after 4 months of follow-up. The case showed that complete surgical resection of the primary tumor is the best treatment for ectopic ACTH syndrome, if the primary tumor which cause ectopic ACTH syndrome cannot be completely cured, it is particularly important to control hypercortisolemia and prevent its complications. This article purports to report this case and review the relevant literature.

Keywords: Case report; ectopic ACTH syndrome; neuroendocrine tumors

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Introduction

Ectopic adrenocorticotropic hormone (ACTH) syndrome refers to symptoms of tumors outside the pituitary gland secreting large amounts of ACTH, prompting bilateral adrenal glands to produce excessive cortisol, which then causes a series of clinical manifestations of Cushing's syndrome. Ectopic ACTH syndrome is rare clinically, accounting for around 5–10% of all Cushing's syndrome (1). Among the tumors that cause ectopic ACTH syndrome, neuroendocrine tumors of intrathoracic (bronchial and thymus) and gastrointestinal pancreatic ones are the most common, while others include small cell lung cancer, pheochromocytoma, and medullary thyroid carcinoma (2-4). This article reports a case of ectopic ACTH syndrome caused by thymic neuroendocrine tumor, and reviews its relevant literature. We present the following case in accordance with the CARE reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-21-86/rc).

Table 1 Changes in ACTH and cortisol

Time point of admission	ACTH (Pg/mL)	Cortisol (nmol/L)				
		8 am	4 pm	Midnight	Low-dose dexamethasone suppression test	High-dose dexamethasone suppression test
11 M before admission (preoperative)	70.63	1,153.16	984.1	1157.98	Not suppressed	Not suppressed
10 M before admission (after surgery)	9.45	343.12	280.93	–	–	–
1 M before admission	70.54	1,105.56	847.22	–	–	–
After admission	76.87	1,133.68	1,160.47	–	975.78 (not suppressed)	684.75 (not suppressed)

M, months.

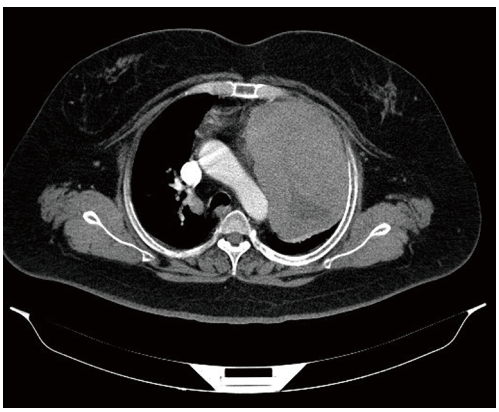

Figure 1 Enhanced CT scan of chest: a mass next to the left mediastinum, about 12.8 cm × 8.4 cm.

Case presentation

A 36-year-old female was admitted to our hospital. 18 months before admission, the patient's menstrual flow decreased significantly which did not improve after treating with traditional Chinese medicine at the local hospital. One year before admission, the patient presented with weight gain (increased by 20 kg within 2 months), rounded face, purple streaks in lower abdomen and groin area, accompanied with puffiness throughout the body, hair loss and acne on face, neck, upper chest. The patient had no history of steroid usage, and no personal and family history of multiple endocrine neoplasia type 1.

Then 11 months before admission, the patient visited a local hospital and her blood pressure increased to 180/100 mmHg. The endocrinological data are showed in *Table 1*. Blood routine: WBC 15.13×10^9/L, N 12.66×10^9/L, N 83.6%; fasting blood glucose 8.1 mmol/L, HbA1c 8.8%; potassium 3.3 mmol/L; thyroid function test: normal; magnetic resonance imaging (MRI) of the pituitary: the right pituitary gland is thinner than the left. Chest CT: A soft tissue density mass is seen next to the left mediastinum, with a maximum slice size of about 12.8 cm × 8.4 cm and a CT value of about 47 HU. Enhanced CT scan of the chest: a mass next to the left mediastinum, suspecting thymoma (see *Figure 1*). CT scan of bilateral adrenal glands: no obvious abnormalities were seen. Bone density: osteoporosis. She was diagnosed with ectopic ACTH syndrome and possible thymoma. Ten months before admission, median sternotomy, excision of the left upper mediastinal tumor, and enlarged thymectomy were performed at the local hospital. Pathological diagnosis was type B1 thymoma. ACTH and cortisol decreased after the surgery (see Table1). Weight loss was about 15 kg within 3 months after the surgery. Acne on the face, neck and upper chest disappeared, and puffiness subsided. Three months after surgery, menstrual flow began to recover, with normal cycle, and blood pressure fluctuations were monitored at 110–140/70–90 mmHg. Five months before admission, patient experienced edema in both lower extremities again, and patient's blood pressure increased to 150–170/90–110 mmHg, accompanied by weight gain (10 kg within 2 months), facial acne, irregular menstruation. One month before admission, endocrinological data at the local hospital showed increase of ACTH and cortisol (*Table 1*). Chest CT: the mediastinal showed changes after thymoma resection, and the left adrenal gland thickened as before, considering hyperplasia. Pituitary-enhanced MRI: No obvious abnormalities were seen. The patient was then referred to the Department of Endocrinology in our hospital.

Physical examination on admission: T: 36.8 ℃; P:

105 times/min; R: 25 times/min; BP: 142/102 mmHg; height: 158 cm; weight: 84 kg; waist: 120 cm; BMI: 33.64 kg/m^2. The patient showed full moon face, and multiple acne on the face and fat pads can be seen on the back of the neck and on the bilateral supraclavicular fossa. The heart rate was 105 beats per minute, with uniform rhythm and no murmur was heard. Multiple vertical purple stripes can be seen on the lower abdomen. Moderately edema can be seen in both lower extremities.

Auxiliary examination after admission: blood routine: WBC 15.4×10^9/L, N 89.7%. Biochemical: glutamyl transferase 62 U/L, alkaline phosphatase 119.0 U/L, glucose 6.70 mmol/L, creatinine 63 umol/L, potassium 4.0 mmol/L. Low-dose dexamethasone suppression test and high-dose dexamethasone suppression test are not suppressed (see *Table 1*). PET-CT: No obvious signs of tumor recurrence in the thymus area; multiple hypermetabolism nodules in the bilateral brachiocephalic space and mediastinal space between anterior trachea and posterior vena cava, considering the possibility of lymph node metastasis; multiple bone destruction, increased metabolism, accompanied by L3 pathological fracture, consider multiple bone metastases. The surgery specimens of the local hospital was sent to our hospital's pathology department for consultation, receiving diagnosis: (left upper mediastinal tumor): neuroendocrine tumor, atypical carcinoid; immunohistochemical expression: CK (pan) (++), Ki67 (6% +), CgA (++), CD56 (++), SY (++), ACTH (−). Under CT guidance, L3 vertebral body attachment biopsy on the left side of the vertebral body was performed, and the pathological diagnosis was as the follows: through puncture tissue, the interstitial area saw infiltration of atypical epithelioid cells, consistent with neuroendocrine tumors; immunohistochemistry: Ki67 (30% +), CK (pan) (+++), CD56 (+++), CgA (+), Syn (+++).

Final diagnosis: ectopic ACTH syndrome, thymic neuroendocrine tumor with multiple metastases (lumbar spine, multiple bones? lymph nodes?) after surgery (G3). The patient was administered with sitagliptin and metformin to control blood glucose, with Nifedipine, valsartan and betaloc to lower blood pressure, with potassium chloride to supplement potassium, and with 200 mg of mifepristone twice a day to antagonize the glucocorticoid receptor. After receiving the above treatments, the patient showed improvement in general condition; the systolic blood pressure fluctuated at 130–140 mmHg; acne on the face, neck, and upper chest were better than before, and swelling of both lower extremities was lessened than before. Oncology consultation recommended carrying out systemic chemotherapy of "etoposide and cisplatin" program. The patient was satisfied with the treatment and she requested a referral to the local hospital due to economic reasons.

The patient was followed up for 4 months from discharge to the completion of this paper, mifepristone was continued as well as controlling blood pressure, controlling blood glucose and potassium supplementation. Six courses of "etoposide" single-agent chemotherapy were performed at the local hospital. At the known present moment, the patient's body weight dropped to 76 kg; the puffiness is reduced; the physical strength is better than before; the bone pain is better than before; the systolic blood pressure fluctuated at 120–140 mmHg and the level of fasting blood glucose are acceptable at 6–9 mmol/L.

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

Discussion

This article reports a case of ectopic ACTH syndrome caused by thymic neuroendocrine tumor. Thymus malignancies are a group of relatively rare malignant tumors with an incidence of 0.13/100,000 people in the United States (5). Among primary thymic malignancies, neuroendocrine tumors are the least common, accounting for 2–5% of thymic tumors (6,7).

Symptoms and the degree of symptoms in patients with ectopic ACTH syndrome are related to cortisol levels, the histological type of the tumor, and tumor growth rate (8,9). It has been reported that some intrathoracic neuroendocrine tumors causing ectopic ACTH syndrome grow slowly, and the average interval between the onset of symptoms and clinical diagnosis is 3 years (10). However, the time interval between the early presentation of symptoms and clinical diagnosis in this case is about 10 months. From the decrease in menstruation, the patient progressed to typical Cushingoid features within 8 months, including full moon face, centripetal obesity, hypertension, diabetes, severe hypokalemia and edema, which all suggests that the tumor grows fast and its ability to secrete ACTH is strong.

The localized diagnosis of ectopic ACTH syndrome

requires the use of imaging examinations, mainly including CT and MRI, somatostatin-receptor-based diagnostic imaging and positron emission tomography (PET). CT and MRI examinations are commonly used in the diagnosis of ectopic ACTH syndrome. Studies have shown that CT sensitivity (53%) is higher than that of MRI (37%) (11). Due to the fact that most of the tumors of ectopic ACTH syndrome are located in the chest cavity, it is more economically beneficial to perform chest imaging studies first. In this case, the patient underwent chest CT examination before operation and found a huge mass in the anterior mediastinum. Somatostatin-receptor-based diagnostic imaging include indium-111 (^{111}In) OctreoScans and Ga-68 DOTATATE (or Ga-68 DOTATOC) PET scanning. There are somatostatin receptors on the cell surface of ectopic ACTH-producing tumors, so indium-111 OctreoScans can find some ectopic ACTH-producing tumors (12-14). Some studies have shown that the sensitivity of this method to detect tumors of occult ectopic ACTH syndrome is about 33–53% (11,15,16). Undetectable tumors may be related to tumors that are too small or lack somatostatin receptors. Due to the high false positive rate of octreotide scans, octreotide scans need to be combined with CT or MRI to confirm the lesions (17). Studies have shown that in some patients with occult ectopic ACTH syndrome who did not find tumors on CT and/or MRI, 18F-FDG PET scans also did not find tumors (11), which may due to the low metabolic rate of these tumors. Considering economic-benefit factors, 18F-FDG PET scan is not recommended as a routine examination. In some cases, 18F-FDG PET scans found tumors that were not found by other imaging studies, or had certain value in confirming suspected lesions and tumor recurrence (18-20). In the case of this article, the patient suspected tumor metastasis or recurrence after surgery, and 18F-FDG PET scan then embodies its diagnostic advantages.

Complete removal of the primary tumor is the most ideal treatment for ectopic ACTH syndrome, because of the fact that it can remove the source of ectopic ACTH secretion and improve metabolic abnormalities. Studies have shown that even after surgical resection and perioperative adjuvant therapy, local recurrence and distant metastasis are more common in thymic neuroendocrine tumors (21). In this paper, although the patient's thymic neuroendocrine tumor was immunohistochemically negative for ACTH, the symptoms of Cushing's syndrome improved after thymic neuroendocrine tumor resection, and the levels of blood ACTH and cortisol decreased, all supporting the tumor as the ectopic ACTH secretion source. This patient had a large thymic neuroendocrine tumor, and the expression level of ACTH might be different in different areas of the tumor, which might in turn become the cause of immunohistochemical negative for ACTH. The patient's symptoms of Cushing's syndrome recurred within 1 year after surgery; the levels of blood ACTH and cortisol increased again, and multiple distant metastases were found. When the primary tumor cannot be completely removed, and in cases where hypercortisolemia cannot be controlled by other methods, including ineffective or intolerant medical treatment, the patient refusing medical treatment, young women want to become pregnant, and long-term follow-up cannot find the primary tumors and other conditions, unilateral or bilateral adrenalectomy is also one of the options (8).

The drug treatment of ectopic ACTH syndrome mainly includes cortisol synthesis inhibitors, glucocorticoid receptor antagonists, dopamine receptor agonists and somatostatin analogs. Cortisol synthesis inhibitors are the main therapeutic drugs to control the side effects of hypercortisolemia. At the present, these drugs mainly include ketoconazole, metyrapone, mitotane, etomidate (22). Etomidate, an injection, can be used in patients with severe ectopic ACTH syndrome who needs quick control of hypercortisolemia (23). Mifepristone is a progesterone receptor antagonist, which can antagonize the glucocorticoid receptor at higher doses at 300–1,200 mg daily. Because mifepristone blocks the effect of glucocorticoids, blood ACTH and cortisol levels will rise (24), so blood ACTH and cortisol tests cannot be used to evaluate its efficacy and adrenal insufficiency. In this case, the symptoms of ectopic ACTH syndrome improved after treatment of mifepristone. Some tumors that cause ectopic ACTH syndrome have dopamine receptors and somatostatin receptors, so dopamine receptor agonists and somatostatin analogs can be used alone or in combination for tumor recurrence, incomplete resection, or occult sources of unknown origin (8). Octreotide and/or cabergoline have been successfully used in the treatment of some patients (25-27). In our case, because of the availability of drugs and the economic reasons of the patient, we used mifepristone to antagonize the glucocorticoid receptor. The patient showed improvement in general condition and we recommended carrying out systemic chemotherapy of "etoposide and cisplatin" program.

With high expression of somatostatin receptors on

some ectopic ACTH-producing neuroendocrine tumors (as determined by somatostatin-receptor-based diagnostic imaging), peptide receptor radionuclide therapy (PRRT) is in turn one of its treatment options. The radionuclide chelates with the peptide ring to form a targeted radiopharmaceutical (such as the radiolabeled somatostatin analog ^{177}Lu-dotatate), which binds to the somatostatin receptor highly expressed on the surface of neuroendocrine tumor cells and internalizes into the tumor cells transmitting lethal radionuclides to maintain a high concentration of radionuclides in tumor cells (28). ^{177}Lu-dotatate was successfully used to treat some gastrointestinal pancreatic neuroendocrine tumors (29). In 2018, it was approved by the FDA for the treatment of adult somatostatin receptor positive gastrointestinal pancreatic neuroendocrine tumors. However, ^{177}Lu-dotatate is relatively limited for thymic neuroendocrine tumor therapy (30). For patients with neuroendocrine tumors with high uptake of somatostatin receptor imaging that has failed treatment with somatostatin analogs, the effectiveness of PRRT treatment has been initially confirmed. Currently, PRRT is mostly suitable for patients with unresectable and/or metastatic and well-differentiated G1 and G2 neuroendocrine tumors. Well-differentiated G3 neuroendocrine tumors may benefit from this specific technique (more PRRT treatment response rates and clinical data needed) (31).

In addition, interferon therapy and chemotherapy (cisplatin, etoposide, 5-fluorouracil, streptozotocin, doxorubicin, etc.) can be used for the treatment of metastatic neuroendocrine tumors and small cell lung cancer (4,32), sorafenib can be used for immunotherapy of medullary thyroid cancer (33). External radiotherapy has been used to treat some carcinoid tumors (4,34). Surgical resection of liver metastases, cryoablation, hepatic arterial chemoembolization, and liver transplantation all have been used to treat neuroendocrine tumors with liver metastases (35). When surgery and traditional treatments fail, the above multidisciplinary treatments shall be considered for treatments.

The prognosis of ectopic ACTH syndrome factors to the histological type of the tumor and the severity of hypercortisolemia, as both will affect mortality and complications. Although some patients with indolent tumors survive for many years, most patients with obvious tumor metastasis will succumb to demise within 1 year. Patients with small cell lung cancer, medullary thyroid carcinoma, and gastrinoma have poorer prognosis (4,34). Patients with occult ectopic ACTH syndrome who have timely and effective control of hypercortisolemia have a relatively long survival period (4,36). Hypercortisolemia is associated with infection, pancreatitis, peritonitis, meningitis, heart failure, and pulmonary embolism, all of which can be the cause of death (4,34,37). Hypercortisolemia can be controlled by drugs or adrenalectomy, so all patients should not suffer consequences of long-term continuous hypercortisolemia. In this article, the patient with ectopic ACTH syndrome found multiple metastases after surgical resection of thymic neuroendocrine tumor. Mifepristone was given to antagonize glucocorticoid receptor at the same time as systemic chemotherapy. After 4 months of follow-up, her body weight decreased, and the edema and bone pain were alleviated. The physical strength is better than before, and blood pressure and blood glucose control are at acceptable range. Longer-term outcomes await further follow-up.

Conclusions

This article reports a case of ectopic ACTH syndrome caused by thymic neuroendocrine tumor. Both neuroendocrine tumors and non-endocrine tumors might be related to ectopic ACTH syndrome. The most common causes of ectopic ACTH syndrome are neuroendocrine tumors derived from the intrathoracic (bronchial and thymus) and gastrointestinal pancreas. Complete surgical resection of the primary tumor is the best treatment for ectopic ACTH syndrome. If there's no chance of surgery or surgical treatment fails, multidisciplinary comprehensive treatment shall be attempted. The prognosis of ectopic ACTH syndrome is related to the histological type of the tumor and the severity of hypercortisolemia. If the primary tumor cannot be completely cured, it is particularly important to control hypercortisolemia and prevent its complications.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-21-86/rc

Conflicts of Interest: All authors have completed the

ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-21-86/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the editorial office of this journal.

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