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Ectopic Adrenocorticotropic Hormone Syndrome: A Case Report and Literature Review

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Abstract

Introduction: ACTH syndrome is an uncommon disease. In this study, we probed into the clinical manifestation, diagnosis and treatment of ectopic adrenocorticotropic hormone (ACTH) syndrome from a case.

Case description: A middle-aged female was clinically manifested by hypertension, high blood glucose, large face and high body weight as well as plethora. The plasma cortisol and serum ATCH levels of the patient were significantly elevated, which could not be inhibited by large or small doses of dexamethasone suppression tests. Thoracic computed tomography indicated space occupying lesion in the middle lobe of right lung. Surgical resection confirmed that the lung mass was "atypical carcinoid", which secreted ACTH and belonged to a tracheal-pulmonary neuroendocrine tumour. The symptoms were largely alleviated after operation.

Discussion and Conclusion: Surgical resection was an effective approach for ectopic ATCH syndrome. The Etiology of most patients clinically manifested with Cushing syndrome (CS) is Cushing disease (CD). In this study, we presented a rare case report of a patient who was clinically manifested with ectopic adrenocorticotropic hormone (ATCH) syndrome (EAS) due to secretion by pulmonary tumour.

Keywords: ACTH; Lung cancer; Cushing syndrome

Introduction

Ectopic Cushing syndrome is a form of Cushing syndrome in which a tumour outside the pituitary gland produces a hormone called adrenocorticotropic hormone (ACTH). It occurs when the pituitary gland makes too much of the hormone ACTH. ACTH then signals the adrenal glands to produce too much cortisol. Symptoms include rapid weight gain, particularly of the trunk and face with sparing of the limbs. Elevated levels of total cortisol can also be due to estrogen found in oral contraceptive pills that contain a mixture of estrogen and progesterone, leading to Pseudo-Cushing's syndrome. In this study, we probed into the clinical manifestation, diagnosis and treatment of ectopic adrenocorticotropic hormone (ACTH) syndrome from a case.

Case Description

A middle-aged female was discovered with hypertension in physical examination more than three years ago. Her face became rounder, accompanied by complexion redness more than two years ago, along with dizziness, fatigue, palpitation, fat thickening in abdomen, neck, back. The patient appeared beard around lip more than one year ago. The patient was admitted to the department of endocrinology of our hospital in April 2014, and was diagnosed with hypertension, hyperglycaemia. Plasma cortisol was 538.90 nmol/L (8:00 AM), serum ATCH was 140.80 pg/m (16:00). Pituitary dynamic enhanced magnetic resonance imaging (MRI) did not indicate any no obvious abnormalities. Thoracic computed tomography (CT) indicated nodule lesion in the middle lobe of right lung, while tumour could not be excluded.

The clinical symptoms of the patient were relieved after symptomatic treatment, including decreasing blood sugar and blood pressure. The patient was admitted to the department of endocrinology of our hospital again in August 2016 due to worsened symptoms. Cortisol rhythm assay indicated 1709.00->1750–1180 nmol/L (8: 00-16: 00-0: 00). ATCH assay demonstrated 111.30- 97.22-79.82 pg/mL (8: 00-16: 00-0: 00), potassium was 3.00 mmol/L. Overnight low-dose dexamethasone suppression test was negative. Taken together, the patient could be diagnosed with ACTH-dependent Cushing's disease. Patients underwent standard high-dose dexamethasone suppression test, which was negative, hence, she was prone to be diagnosed with ectopic ACTH-dependent hypercortisolism. Thoracic three-dimensional dynamic contrast-enhanced CT scan indicated nodule lesion in the middle lobe of the right lung, which was slightly larger than before and was more likely to be a benign tumour (Figure 1). Afterwards, the patient was transferred to department of thoracic surgery, followed by surgical resection of the pulmonary lesion. Postoperative pathology demonstrated neuroendocrine tumour, which was considered as atypical carcinoid (Figure 2). Postoperative ATCH was 7.32 pg/mL, cortisol was 247.70 nmol/L, blood pressure was 127/83 mmhg, potassium was 4.40 mmol/L. The patient recovered well after operation. She followed up for 6 months after discharge and there was no obvious abnormality.

Discussion

CS, also known as hypercortisolism, is a syndrome caused by various etiologies, which acts on target organs. Its typical manifestations include centripetal obesity, hypertension, abnormal glucose metabolism, hypokalaemia and osteoporosis [1]. CS can be divided into ACTH-dependent CS and ACTH-independent CS. ACTH-dependent CS mainly includes CD, ectopic ACTH syndrome (EAS) and ectopic CRH syndrome. Among them, CD is the most common cause [2], and EAS can be categorized into slow progression and rapid progression according to the degree of malignancy. ACTH-independent CS mainly

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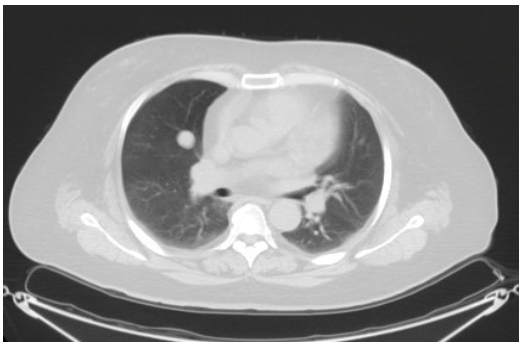

Figure 1: Chest-enhanced CT indicated solid nodules in the middle lobe of right lung, which was 16 × 17 mm in size, of central type, with smooth surface.

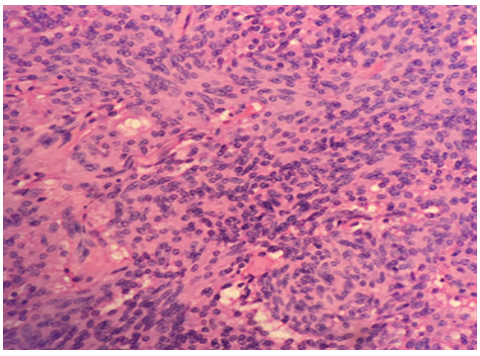

Figure 2: Postoperative pathological examination indicated (the middle lobe of right lung) that tumor cells were fusiform or round, distributed in nest-like pattern. The chromatin of nuclei was relatively delicate, with inobvious nucleoli. The nuclear splitting was approximately 2/10 HPF, without necrosis. Combined with immunohistochemical results, it was consistent with neuroendocrine tumors. Together, it was considered as atypical carcinoid (2 cm of diameter), without involvement of the bronchial stump. Immunohistochemical analysis: CK(+), Vim (-), S-100 (-), SOX-10 (-), Syn (+), CgA (+), CD56 (+), TTF-1 (+), p63 (+), Calretinin (-), CD34 (-).

includes adrenocortical adenoma (ACA), adrenocortical carcinoma (ACC), ACTH-independent macronodular adrenocortical hyperplasia (AIMAH), primary pigmented nodular adrenal corticospasm (PPNAD), ectopic cortisoloma (ECA) [3]. Relevant epidemiology indicates that the CS incidence ratio of male and female is 1: 3, while the EAS incidence ratio of male and female is 1: 1.35 [4]. In women with CS, the incidence ratio of CD and EAS is 9:1, which is 2:1 in men with CS [5].

According to the latest WHO classification of lung cancer [6], broncho-pulmonary neuroendocrine tumor (BPNET), accounts for 1-2% of lung tumours, including large cell neuroendocrine carcinoma (LCNEC), small cell lung cancer (SCLC), typical carcinoid (TC) and atypical carcinoma (AC). The common characteristics of BPNET are as follows [7]:

1. BPNET harbours neuroendocrine morphology, including organ-like, rosette-like, peripheral palisade-like and trabecular-like arrangement.
2. BPNET is positive for neuroendocrine marker, among them, chromogranules protein, synaptophysin and CD56 (N-CAM) are commonly used with relatively high sensitivity and specificity. The pathological result of the case discussed in this study was atypical carcinoid, which belonged to moderately malignant neuroendocrine tumours [8]. The tumour was able to secrete ACTH, therefore, it was EAS.

The typical CS is commonly manifested as centripetal obesity, full moon face, plethora, purple striae etc. In addition, in severe patients caused by cancer, they generally present with body weight loss, hypertension, edema, hypokalaemia alkalosis etc., which are serious and progress rapidly. In this case report, we presented a patient with EAS, hence, we discuss EAS and CD, the most common CD.

According to relevant literature [9], from the clinical manifestations, compared with EAS, CD more commonly presents with chronic hypercortisolism with a history over 1-2 years, including thin skin, generally accompanied by purple striae, increased vascular fragility (slight injury can cause ecchymosis) and muscle consumption (muscle injury in the proximal limb). On the contrary, compared to CD, EAS harbours a shorter history, and unapparent clinical manifestation. However, the clinical manifestations of part of EAS patients (usually well-differentiated pulmonary endocrine tumours) are consistent with those of typical CD. In terms of biochemical indicators, the ACTH, urinary 17-hydroxy corticosteroids, urinary 17-ketocorticosteroids, blood and urine levels of cortisol are higher in EAS patients, the majority of whom, cannot be inhibited by large doses of dexamethasone suppression test [10]. In addition, they are generally accompanied by hypokalaemia [10]. Plasma CRH levels are higher in CD patients, and the sensitivity of this indicator is up to 85-90% [11]. Another literature [12] demonstrates that POMC facilitates in identification of EAS and CD, the plasma POMC level is higher in the former. The bilateral inferior petrosal sinus sampling (BIPSS) is helpful in accurately qualitative and positioning diagnosis of CD, which plays an extremely important role in diagnosis and treatment of CD. In the case of an ACTH ratio of >2.0 between the inferior petrosal sinus (iPS) and the peripheral (pefipher-a1), it is considered as CD, while in the case of ratio of <2.0, it is more likely to be EAS [13]. In patients with ACTH-dependent CD, MRI is the most effective imaging examination. Pituitary MRI generally indicates the presence of pituitary microadenomas in CD patients. While in EAS patients, space occupying lesions are generally discovered in lungs, pancreas, thyroid and gastrointestinal tract by imaging examination according to relevant literature [14], which can be further confirmed as ACTH-secreting neuroendocrine tumours. Among them, pulmonary or bronchial tumours approximately account for 50%, thymus and pancreatic tumours approximately account for 10%, and PET-CT is also of significant value in qualitative diagnosis of lung cancer [15].

For the treatment of CD and EAS, first-line treatment is surgical resection of lesions [16]. Transsphenoidal surgery is preferred for CD patients, while surgery is chosen in EAS after accurate positioning of the lesion. For benign unilateral adrenal tumours, surgical removal of unilateral lesions should be performed; for bilateral adrenal nodules hyperplasia, bilateral adrenalectomy and drug treatment are chosen; for primary pigmented nodular adrenocortical disease (PPNAD), laparoscopic bilateral adrenalectomy is preferred. In this case, the tumour was in the upper lobe of the right lung, the cardiopulmonary function of the patient was acceptable, who was tolerant of surgery, therefore, surgical resection of upper lobar lesion in the right lung under thoracoscopy was performed. The operative effect was good, and the patient recovered well. Perioperative management plays a crucial role in the surgical treatment of thoracic surgery [17].

Conclusion

Routine inhalation of glucocorticoid+bronchodilator and

intravenous infusion of mucus dissolving agent are recommended before operation and 3-7d after operation, to reduce the surgical risk and postoperative complications. For CS which cannot be excised or completely resected, corresponding second-line treatment can be adopted: bilateral adrenalectomy can be adopted in EAS with metastasis and under poor control by drugs in a short period; a second trans-sphenoidal approach surgery can be conducted in the case of incomplete resection of lesion in the first try in CD patients; for patients with CD and EAS who fail in surgery or experience recurrence, it is recommended to perform radiotherapy, and the commonly used drugs are pasireotide, ketoconazole and etc. [18]. In addition, steroid biosynthesis inhibitors are recommended under the following circumstances: in CD patients who have undergone transsphenoidal surgery (irrespective of whether they have received radiotherapy or not), in EAS patients with metastases, in patients with adrenocortical cancer, in adjuvant therapy to reduce plasma cortisol levels.

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