Case Report

Ectopic adrenocorticotrophic hormone syndrome initially presenting as abnormal mental behavior caused by thymic carcinoid: a case report

Xu Han[#], Qihe Liu[#], Yan Yang, Xixian Ke, Cheng Chen

Department of Thoracic Surgery, The Affiliated Hospital of Zunyi Medical University, Zunyi, China

[#]These authors contributed equally to this work.

Correspondence to: Xixian Ke; Cheng Chen. Department of Thoracic Surgery, The Affiliated Hospital of Zunyi Medical University, 149 Dalian Road, Zunyi 563000, China. Email: kexixian@zmu.edu.cn; 29217036@qq.com.

Background: Thymic carcinoid is a rare highly differentiated neuroendocrine neoplasm, which can manifest as endocrine disorders caused by ectopic adrenocorticotrophic hormone (ACTH) syndrome. Although clinical manifestations such as hypertension and hypokalemia are common manifestations in patients with ectopic ACTH syndrome, clinicians should also be aware of the mental and behavioral abnormalities that may initially appear in patients. It is extremely rare for patients with ectopic ACTH syndrome caused by thymic carcinoid to concurrently exhibit abnormal mental behavior, especially as the initial clinical manifestation of the tumor. Studies have suggested that abnormal mental behavior may be related to elevated blood cortisol levels.

Case Description: A patient was admitted to hospital due to abnormal mental behavior, manifesting as hyperphasia involving gibberish and illogical language, trance, and a state of suspicion. The patient had experienced persecutory delusion. Auxiliary examination revealed elevated cortisol and ACTH. Chest computed tomography (CT) showed right anterior mediastinal tumor. After discussion, the multi-disciplinary team (MDT) concluded that ectopic ACTH syndrome derived from the thymus should be considered. After excluding surgical contraindications, a thymic tumor was resected, and the postoperative pathology confirmed that it was thymic carcinoid. At 6 postoperative months, the results were as follows: cortisol at 8:00 am 196.50 nmol/L; and ACTH at 8:00 am 28.63 pg/mL. The patient's mental behavior had returned to normal, and normal communication was possible. The postoperative symptoms and signs of the patient were improved, which reiterated the presence ectopic ACTH syndrome caused by thymic carcinoid.

Conclusions: Thymic carcinoid with ectopic ACTH syndrome is very rare in clinical practice, and it is easily missed and misdiagnosed. Although clinical manifestations such as hypertension and hypokalemia are common manifestations in patients with Cushing's syndrome, clinicians should be aware that patients with Cushing's syndrome may initially exhibit abnormal mental behavior. Clinically, if the patient exhibits abnormal mental behavior accompanied by symptoms such as hypokalemia, hypertension, and diabetes, blood cortisol and ACTH hormone levels should be screened without delay. If the levels are found to be significantly increased, ACTH syndrome should be highly suspected.

Keywords: Thymic carcinoid; ectopic adrenocorticotrophic hormone syndrome (ectopic ACTH syndrome); multi-disciplinary team (MDT); case report

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Introduction

Ectopic adrenocorticotrophic hormone (ACTH) syndrome is a special type of Cushing's syndrome, which was firstly proposed by Liddle (1) in 1963. It refers to the excessive secretion of ACTH by non-pituitary tumor tissues, which stimulates adrenal cortex hyperplasia and makes it secrete excessive cortisol, causing a series of clinical syndromes. Ectopic ACTH syndrome is rare in clinical practice, accounting for about 12–17% of the total number of patients with Cushing's syndrome. The most common primary tumor causing this syndrome is thoracic tumor (2-4). Thymic tumor is a type of thoracic tumor, accounting for 0.2–1.5% of adult malignancies, 20% of all mediastinal tumors, and 50% of all anterior mediastinal tumors. Thymic tumors can secrete a variety of bioactive substances, which can result in different paraneoplastic syndromes, including myasthenia gravis, limbic encephalitis, pure red-cell anemia, or Cushing's syndrome, among others. Surgical resection of primary tumors is the best treatment for paraneoplastic syndromes (5,6). Thymic carcinoid is a rare thymic tumor, which is usually attributed to large tumors, also known as highly differentiated neuroendocrine neoplasms. According to its morphology, it can be divided into typical carcinoid and atypical carcinoid. Thymic carcinoid can also secrete ACTH, resulting in ectopic ACTH syndrome, and causing electrolyte and metabolic abnormalities in patients. Its clinical manifestations can include typical Cushing's syndrome manifestations such as central obesity, moon-shaped face, skin ecchymosis, purple skin striae, skin pigmentation, hypertension, hyperglycemia, hypokalemia, and others (7-10). It is extremely rare for patients with ectopic ACTH syndrome caused by thymic carcinoid to concurrently exhibit abnormal mental behavior, especially as the initial clinical manifestation of the tumor and can be manifested as insomnia, memory disorders and so on. It easily misdiagnosed as mental disorders and can be extremely resistant to medical therapy. A previous study suggested that abnormal mental behavior may be related to elevated blood cortisol levels (11). Early localization and appropriate surgical resection of the ectopic ACTH-secreting tumour can be of immense value to the successful alleviation of the psychotic episodes of the patients with ectopic Cushing's syndrome (12).

Recently, our department diagnosed and treated a patient admitted to hospital due to abnormal mental behavior. It initially misdiagnosed as mental disorders. The final pathological diagnosis was ectopic ACTH syndrome caused by thymic carcinoid. We present the following case in accordance with the CARE reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-22-173/rc).

Case presentation

A 25-year-old male patient was admitted to hospital after his family noticed that his mental behavior had been abnormal for more than 10 days, manifesting as hyperphasia involving gibberish and illogical language, trance, and a state of suspicion. The patient had experienced persecutory delusion, but was able to recognize people and objects. In the previous 6 months, his weight had increased by about 5 kg. The patient was unconscious, and did not cooperate with physical examination at admission. A moon-shaped face and abdominal obesity were observable. Scattered skin scars and rashes were visible on the skin of the whole body, with purple striae on the abdomen (*Figure 1*). The patient had no prior family history of a similar presentation.

The auxiliary examination upon admission included the following: chest computed tomography (CT): right anterior mediastinal tumor, indicating that thymoma should be considered, the maximum cross section was about 8.1 cm × 9.0 cm, and the enhanced scan was obviously enhanced (*Figure 2*). Pituitary magnetic resonance imaging (MRI): cyst or microadenoma at the posterior edge of pituitary stalk, with uneven signal on enhanced scan. Bilateral adrenal CT: bilateral adrenal thickening. Double renal artery color Doppler ultrasound, thyroid color Doppler ultrasound and electroencephalogram: no obvious abnormality was found. Fasting blood glucose was 20.96 mmol/L; 2-hour postprandial blood glucose was 26.08 mmol/L; cortisol at 12:00 am was >1,750.00 nmol/L; ATCH at 12:00 am was 394.90 pg/mL; cortisol at 8:00 am was >1,750.00 nmol/L; ATCH at 8:00 am was 369.20 pg/mL; cortisol at 4:00 pm was >1,750.00 nmol/L; ATCH at 4:00 pm was 435.10 pg/mL; and urocortisol was 1,421.00 nmol/L. The fluctuation of electrolyte potassium ion before operation was 2.12–3.43 mmol/L (*Table 1*), and the maximum blood pressure was 166/122 mmHg. Both high- and low-dose dexamethasone inhibition tests were negative. Ectopic ACTH was considered to be derived from thymic tumor. Thoracoscopy-assisted thoracotomy thymic tumor resection and mediastinal fat dissection were performed. During the operation, the tumor was located in the anterior upper mediastinum, with a hard texture, size of about 12 cm × 8 cm × 6 cm, complete capsule, and white sarcoma-like

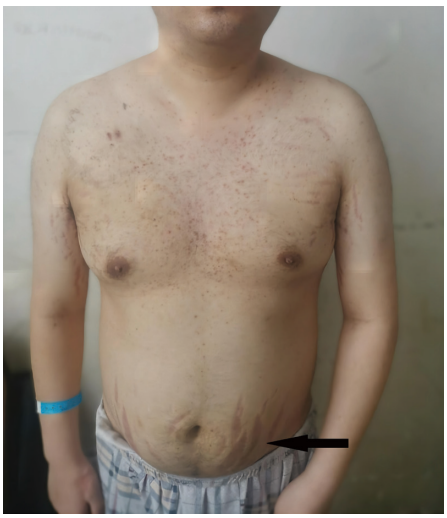

Figure 1 Physical signs of patient at admission. Black arrow points to abdominal obesity and abdominal striae.

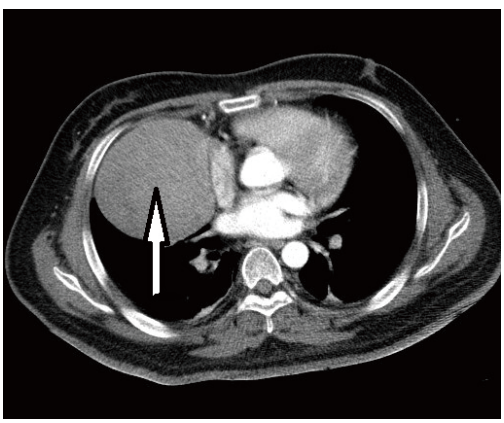

Figure 2 Chest CT of patient before operation. White arrow points to right anterior mediastinal. CT, computed tomography.

appearance, and complete resection was achieved (*Figure 3*). Postoperative pathological examination (*Figure 4*): typical carcinoid, and immunohistochemical (IHC) results showed that the tumor cells had the following characteristics: CK (++), CD56 (++), CgA (+), Syn (++), CD117 (scattered +), CD5 (–), Ki-67 (<2% +), and Vimentin (+). Before surgery, the patient manifesting as hyperphasia involving gibberish and illogical language, trance, and a state of suspicion. And after surgery, the mental behavior of the patient gradually returned to normal. Tests on the first postoperative day returned the following findings: blood potassium 4.32 mmol/L; fasting blood glucose 5.56 mmol/L; cortisol at 8:00 am 360.50 nmol/L; and ACTH at 8:00 am 16.90 pg/mL. And the tumor was removed on chest CT in the third postoperative day (*Figure 5A*). Those on the fourth postoperative day were as follows: blood potassium 4.01 mmol/L; fasting blood glucose 5.26 mmol/L; cortisol at 8:00 am 279.10 nmol/L; and ACTH at 8:00 am 24.57 pg/mL. At 6 postoperative months, the results were as follows: fasting blood glucose 5.12 mmol/L; blood potassium 4.42 mmol/L; cortisol at 8:00 am 196.50 nmol/L; and ACTH at 8:00 am 28.63 pg/mL (*Table 2*). The patient's mental behavior had returned to normal, and normal communication was possible. The abdominal striae had basically disappeared; his weight had reduced compared with that before the operation; blood pressure had returned to normal according to self-examination, and no recurrence was found on chest CT (*Figure 5B*). Timeline of diagnosis, treatment, and prognosis in this case has been presented (*Figure 6*).

Table 1 Preoperative laboratory examination

Feature	Numerical value
Fasting blood glucose	20.96 mmol/L
2-hour postprandial blood glucose	26.08 mmol/L
Cortisol at 12:00 am	>1,750.00 nmol/L
ACTH at 12:00 am	394.90 pg/mL
Cortisol at 8:00 am	>1,750.00 nmol/L
ACTH at 8:00 am	369.20 pg/mL
Cortisol at 4:00 pm	>1,750.00 nmol/L
ACTH at 4:00 pm	435.10 pg/mL
Urocortisol	1,421.00 nmol/L
Potassium ion	2.12–3.43 mmol/L

ACTH, adrenocorticotrophic hormone.

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 Declaration of Helsinki (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

Thymic carcinoid was first reported and named by Rosai

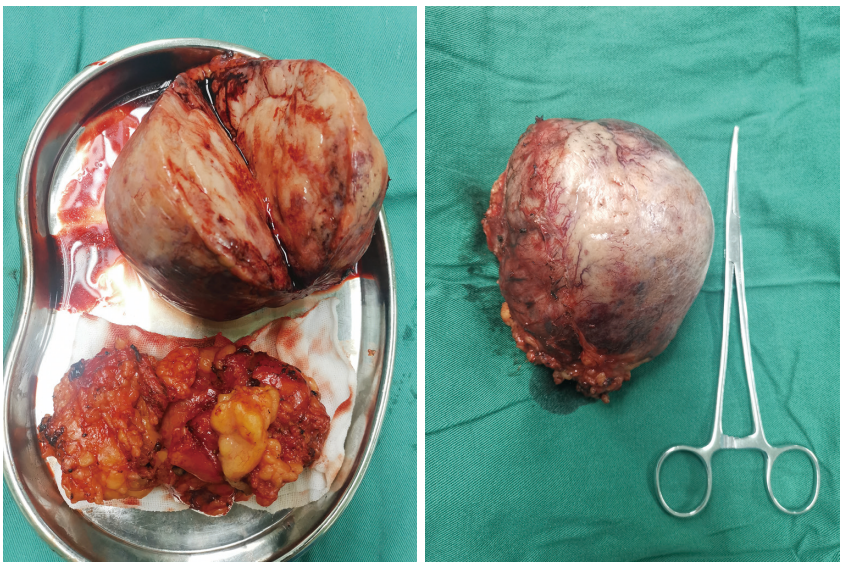

Figure 3 Intraoperative tumor specimen.

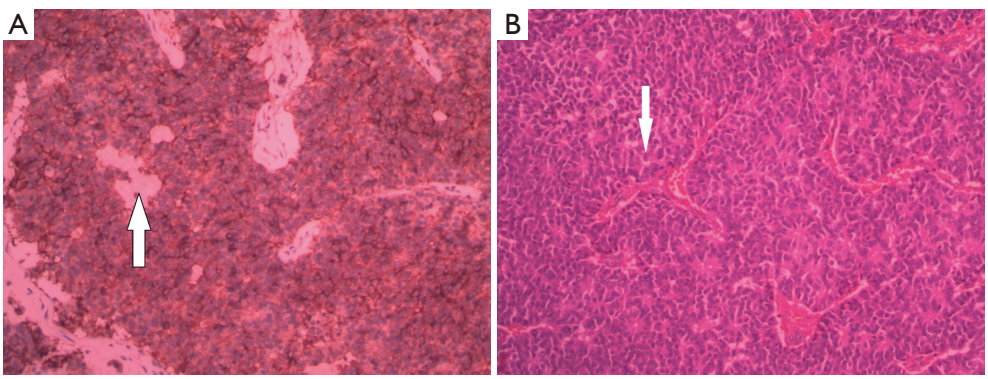

Figure 4 Pathological examination: (A) hematoxylin-eosin staining (×100); (B) immunohistochemistry (×100): CD (++), CgA (+), Ki-67 (<2% +). White arrows point to tumor cell.

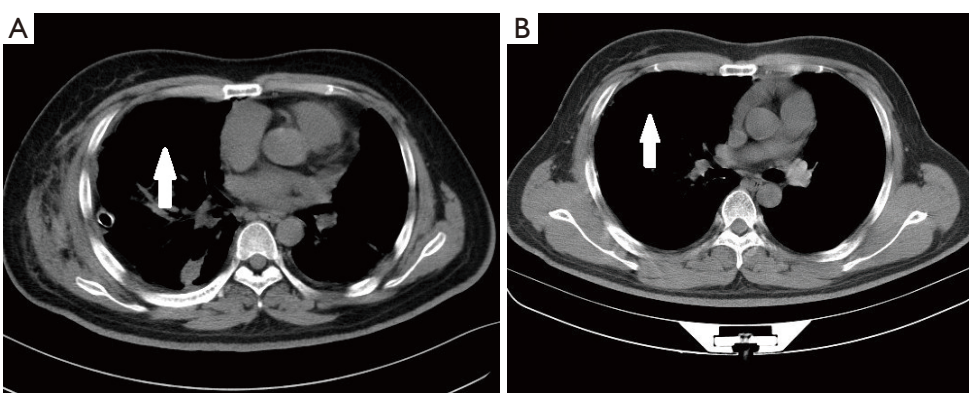

Figure 5 Chest CT of patient after operation: chest CT on POD 3, white arrow points to the tumor was removed (A), and chest CT at 6 months postoperatively, white arrow points to no recurrence was found (B). CT, computed tomography; POD, postoperative day.

Table 2 Postoperative laboratory examination

Feature	POD 1	POD 4	6 months after surgery
Fasting blood glucose	5.56 mmol/L	5.26 mmol/L	5.12 mmol/L
Blood potassium	4.32 mmol/L	4.01 mmol/L	4.42 mmol/L
Cortisol at 8:00 am	360.50 nmol/L	279.10 nmol/L	196.50 nmol/L
ACTH at 8:00 am	16.90 pg/mL	24.57 pg/mL	28.63 pg/mL

POD, postoperative day; ACTH, adrenocorticotrophic hormone.

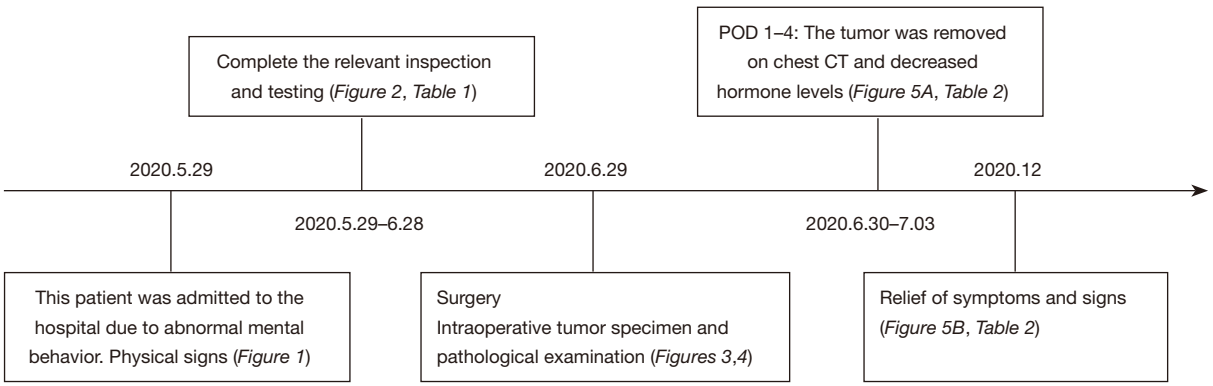

Figure 6 Timeline of diagnosis, treatment, and prognosis in this case (*Figures 1-5*, *Tables 1*,*2*). POD, postoperative day.

and Higa in 1972 (13). It is more common in male patients, and accounts for 2–5% of all thymic tumors. The typical clinical manifestations of thymic carcinoid are compression symptoms such as chest pain, dyspnea, and superior vena cava syndrome. Some patients present atypically and manifest as ectopic ACTH syndrome or other paraneoplastic syndromes that cause endocrine disorders in patients. The intensity of symptoms depends on the blood cortisol level and tumor growth rate. Thymic carcinoid patients presenting with abnormal mental behavior are extremely rare and have been infrequently reported in the literature (5,11,14). Surgical removal of the tumor is the best treatment for ectopic ACTH syndrome caused by thymic carcinoid. Conservative treatment such as drugs is only suitable for patients who have contraindications to surgery or are unwilling to undergo surgery, and the treatment effect is not very good. Studies have shown that the levels of cortisol and ACTH hormones in patients will decrease after tumor removal, and the corresponding symptoms and signs related to hormones can subsequently be relieved and fully resolved (3,14,15).

This patient was admitted to the hospital due to abnormal mental behavior. He had typical Cushing's syndrome manifestations, with moon-shaped face, abdominal obesity, purple abdominal striae, hypertension, hyperglycemia, hypokalemia, and so on. Auxiliary examination found that the patient's blood cortisol and ACTH levels were increased. The chest CT results were suggestive of thymoma. The results of CT revealed bilateral thickening of the adrenal glands. An MRI of the pituitary gland showed a cyst or microadenoma on the posterior edge of the pituitary stalk. After discussion involving the endocrinology, neurology, neurosurgery, imaging, urology, and other multi-disciplinary team (MDT) members, our department concluded that the patient has manifestations of Cushing's syndrome. Adrenal thickening may be a secondary manifestation of ACTH, and the possibility of ectopic ACTH derived from pituitary or thymic tumors is high. Due to the short course of the patient's disease, the likelihood of malignancy was high. High- and low-dose dexamethasone suppression tests can be performed to determine the origin of ectopic ACTH from pituitary or thymic tumors. The tumor can be removed if the source is clear and there are no contraindications. If the postoperative effect is unsatisfactory, adrenalectomy can be used to relieve symptoms. Upon improvement of the high- and low-dose

dexamethasone inhibition test results, it was considered that the patient had ectopic ACTH syndrome derived from the thymus. He had a huge thymic tumor, and his blood cortisol and ACTH levels were elevated. The patient exhibited typical symptoms of Cushing's syndrome and abnormal mental behavior. Surgical removal of the tumor was performed to reduce blood cortisol and ACTH hormone levels, which successfully alleviated the patient's symptoms and signs. After addressing the surgical contraindications, the thymic tumor was removed, and it was pathologically confirmed as thymic carcinoid. On the first and fourth postoperative days, the patient's blood glucose, blood potassium, blood cortisol, and ACTH levels had returned to normal levels. Within half a year, the patient's mental behavior gradually returned to normal, the abdominal striae basically disappeared, and his weight reduced compared to before the operation. These findings reiterated that the patient's disease was ectopic ACTH syndrome caused by thymic carcinoid. Similar cases reported by Okumura (11) also required drugs to help control circulating hormone levels before and after surgery, and the time from the patient's first visit to the diagnosis of ectopic ACTH syndrome was 3 months. In the case of our patient, the first visit to diagnosis interval was only 1 month, which may have been related to the patient's higher hormone levels. Preoperatively, the patient had high blood cortisol and ACTH hormone levels. The high levels of cortisol hormone (>1,750.00 nmol/L) had caused the patient's abnormal mental behavior and may have driven the early response by his family members of sending him to hospital. After admission, the patient was found to have typical Cushing's syndrome and other paraneoplastic syndromes. The ectopic ACTH syndrome of thymic origin was considered after examination, and prompt surgical treatment was carried out, which enables an optimal surgical outcome. His hormone levels returned to normal on the first postoperative day. The symptoms and signs of the patient were gradually relieved and had disappeared after 6 months of follow-up.

In short, thymic carcinoid with ectopic ACTH syndrome is very rare in clinical practice, and it is easily missed and misdiagnosed; however, early diagnosis and treatment have an important impact on prognosis. Therefore, it is vital to improve our understanding of this type of disease and continuously improve diagnostic acuity. Although clinical manifestations such as hypertension and hypokalemia are common manifestations in patients with Cushing's syndrome, the patient's altered mental behavior may have been the reason for his hospital visit. Therefore, clinicians should be aware that patients with Cushing's syndrome may initially exhibit abnormal mental behavior. Clinically, if the patient exhibits abnormal mental behavior accompanied by symptoms such as hypokalemia, hypertension, and diabetes, blood cortisol and ACTH hormone levels should be screened without delay. If the levels are found to be significantly increased, ACTH syndrome should be highly suspected. At the same time, it is necessary to conduct CT or MRI to determine whether there are tumors on the head, chest, or abdomen. If necessary, an MDT can be employed for early diagnosis and early treatment, so as to improve patient prognosis.

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Footnote

Reporting Checklist: The authors have completed the CARE reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-22-173/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-22-173/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 Declaration of Helsinki (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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