Clinical Case Report

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Cushing's syndrome secondary to typical pulmonary carcinoid with mutation in BCOR gene

A case report

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Abstract

Rationale: Typical pulmonary carcinoid is a kind of low-grade malignancy neuroendocrine tumor. Cushing's syndrome is a very rare clinical feature of typical pulmonary carcinoid caused by hypercorticism. Complete tumor resection is the standard curative treatment for primary typical pulmonary carcinoid. However, our knowledge on the gene level of typical pulmonary carcinoid is limited.

Patient concerns: A 42-year-old man was admitted to our hospital for progressive weight gain within one year. No other obvious symptoms were obsessed in this patient. He was clinical diagnosed with ectopic adrenocorticotropic hormone syndrome through hormonal tests and imaging exams. Positron emission tomography-computed tomography detected a pulmonary nodule localized in the middle lobe of the lung and it is thought to be the ectopic source.

Intervention: This patient received a pulmonary wedge resection. After the surgery, a genetic sequencing was performed and it reported a mutation (S1240Cfs*21) in the BCOR gene.

Diagnosis: Postoperative pathology confirmed the diagnosis of ACTH-producing typical pulmonary carcinoid.

Outcomes: The patient had a smooth postoperative course and no recurrence of the tumor was found for 3 years.

Lessons: Mutation in BCOR gene is quite common in pulmonary neuroendocrine tumor and it has been proven to play a role in the development of some tumor. We herein first report BCOR gene mutation in Cushing's syndrome secondary to TPC and it may become a promising therapeutic target in the future.

Abbreviations: 18-F-FDG = 18-fluorine-fluorodeoxyglucose, ACTH = adrenocorticotropic hormone, CT = computed tomography, MRI = magnetic resonance imaging, PET-CT = positron emission tomography-computed tomography, SHH = Sonic Hedgehog pathway, SUV = standardized uptake value, TPC = typical pulmonary carcinoid.

Keywords: BCOR gene mutation, case report, ectopic ACTH syndrome, typical pulmonary carcinoid

1. Introduction

Typical pulmonary carcinoid (TPC) is a kind of low-grade malignant lung tumors that are usually in the central airways of the lung.[1] It usually arises from neuroendocrine Kulchitsky cells located in the bronchial epithelium and comprise between 1% and 2% of all primary lung cancers.[2,3] Surgical resection is the preferred treatment strategy for TPC.[4]

Ectopic Cushing syndrome usually relates to the ectopic adrenocorticotropic hormone (ACTH) syndrome (EAS) and represents approximately 20% of ACTH-dependent and approximately 10% of all types of Cushing syndrome.[5] Nearly any neuroendocrine or non-endocrine tumors may be associated with EAS, among which small cell lung carcinoma, pulmonary carcinoid, and medullary carcinoma of the thyroid are the most common tumors associated with EAS.[6,7] It is hard to tell the difference between EAS and other diseases mainly manifest as Cushing syndrome. Endogenous hypercortisolism (overnight dexamethasone test or low-dose dexamethasone test, urinary free cortisol and midnight serum, or salivary cortisol assessments) and the demonstration of detectable plasma ACTH can be used to exclude primary adrenal disease and corticotropin-releasing hormone test (either alone or in combination with desmopressin).[8] The high-dose dexamethasone test is the most commonly used dynamic tests can help us to exclude pituitary adenomas.[9] Besides, whole-body venous catheterization and imaging test have been proved to be more effective to find the ectopic source.[10]

Although cases of Cushing syndrome secondary to TPC have been reported, detailed information on the gene level is not available. In this report, we present a patient whose initial appearance was Cushing syndrome secondary to TPC. This patient underwent surgical resection of the tumor and had a good prognosis without tumor recurrence for 3 consecutive years.

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Informed Consent: Written informed consent was obtained from the patient to participate to this case report and any accompanying images.

Authors' contributions: WY drafted the manuscript and collect the date. YL is an endocrinologis and involved in interpretation of the criteria of diagnosis. LJ is a pathologist and involved in interpretation of the histological aspect. YM is a genomics specialist and involved in collection and interpretation of the genomics date. All authors read and approved the final manuscript.

The authors declare that they have no conflicts of interest to disclose.

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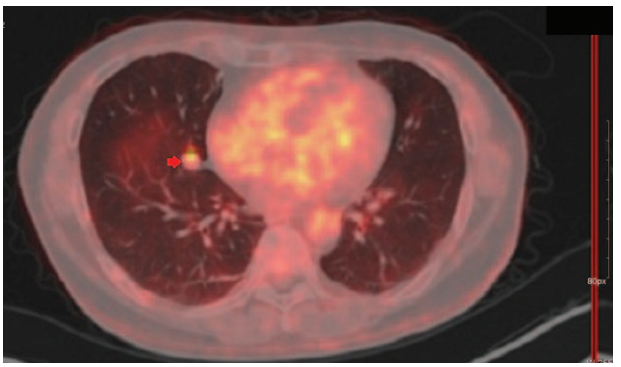

Figure 1. A nodule (early imaging standardized uptake value $[SUV]_{max}=2.80$, delayed imaging $SUV_{max}=5.51$) was detected in the middle lobe of right lung on the PET-CT. This nodule is quite difficult to distinguish with other pulmonary nodules on CT scan. CT = computed tomography, PET-CT = positron emission tomography-computed tomography.

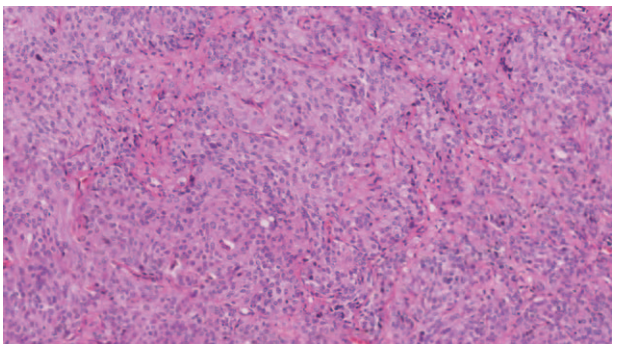

Figure 2. Histopathological examination of the surgical specimen revealed small tumor cell with an unclear boundary arranged in nest bulk with eosinophilic cytoplasm. The mitotic count was 1/10 per high-power field. (Haematoxylin and eosin staining, original magnification ×10).

Interestingly, a genetic sequencing was performed on the patient after surgery and it reported a mutation in the BCOR gene.

2. Case presentation

A 42-year-old man was admitted to our hospital for progressive weight gain within 1 year. Truncal obesity, moon face, and ankle edema were observed on him. In the laboratory tests, the patient's blood pressure, serum potassium, blood glucose level, glucose tolerance, and hypoalbuminemia were all in normal range. No remarkable medical, family, and psychosocial history was observed.

Given his high urine free cortisol level (604.3 μg/d), high midnight serum cortisol level (556.67 nmol/L at 0:00 am), and lack of suppression of serum cortisol after a low-dose (1 mg overnight) dexamethasone suppression test (428.50 nmol/L at 8 am), the patient was diagnosed with Cushing syndrome. During subsequent evaluation, a large-dose dexamethasone (8 mg overnight) also failed to restrain serum cortisol level (607.54 nmol/L at 8 am). In addition, there were no positive changes in brain magnetic resonance imaging (MRI) and inferior petrosal sinus sampling showed that ACTH levels were just 12% higher than that in peripheral blood. These findings led us to exclude Cushing disease. The ACTH levels detected were very high in the monitoring (111 ng/L at 0 am; 132 ng/L at 8 am; 176 ng/L at 4 pm). No abnormalities were detected in abdominal computed tomography (CT) and ultrasound imaging. Adrenal adenoma was then excluded and ectopic ACTH syndrome was tentative diagnosed. In order to find the ectopic source, the patient received a whole body positron emission tomography-computed tomography (PET-CT) with 18-fluorine-fluorodeoxyglucose (18-F-FDG). Finally, a nodule (14 × 10 mm) was detected in the middle lobe of right lung (early imaging standardized uptake value $[SUV]_{max}=2.80$, delayed imaging $SUV_{max}=5.51$)

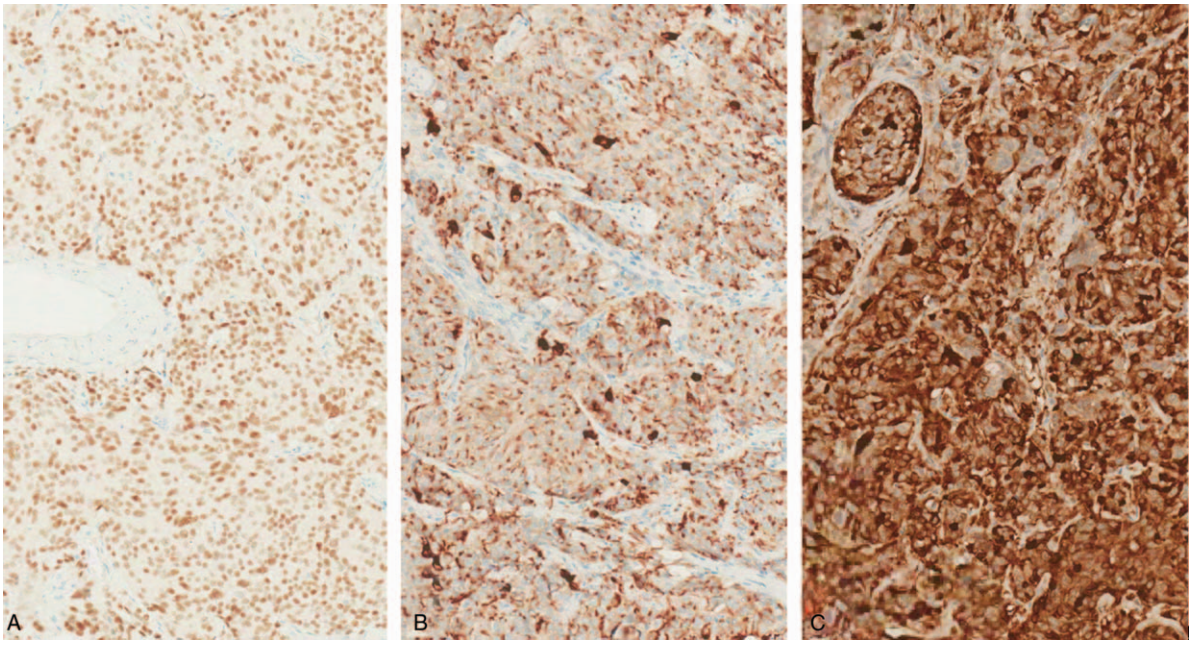

Figure 3. Immunohistochemical staining of the surgical specimen. In part A, the cells are marked by TTF-1. In part B, the cells are marked by CgA. In part C, the cells are marked by ACTH. (Original magnification ×10). ACTH = adrenocorticotropic hormone.

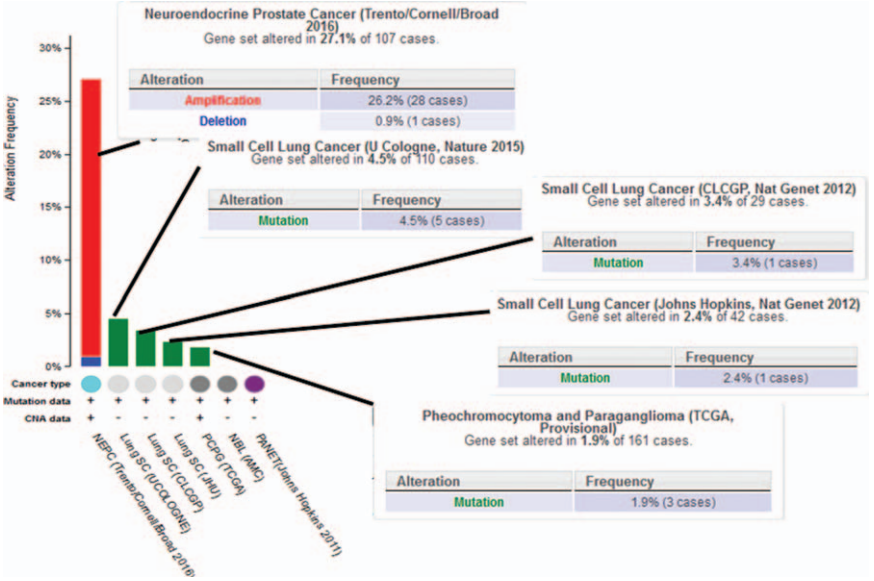

Figure 4. A summary of BCOR gene alterations in neuroendocrine tumor.

(Fig. 1), which indicated ectopic ACTH syndrome was caused by pulmonary neuroendocrine tumor.

After a multi-disciplinary team discussion, this patient received a pulmonary wedge resection. Grossly, the resected mass measured approximately 1×1 cm in size. Histologically, the tumor was primarily made up of epithelioid cells (Fig. 2). Immunohistochemically, the tumor matched the diagnosis of a typical carcinoid. It was highly positive for Syn, CgA, CD56, S-100, ACTH, and TTF-1 (Fig. 3). Whereas, staining for CK7, CK6, and P63 were all negative. The positive staining intensity found for Ki-67 expression was 1%.

A next generation sequencing was performed on the patient according to his request. It showed that a missense mutations in the BCOR gene (Ser1240Cys*21) and KIT (p.I527F) gene existed in the patient, no positive mutation was detected in EGFR gene, ALK gene, MET gene, etc.

The patient did not have any complications postoperatively and was discharged from the hospital on postoperative day 9. The patient did well during follow-up and for 3 consecutive years no recurrence of the tumor was found.

3. Discussion

TPC is a kind of low-grade malignancy neuroendocrine tumors and it accounts for 1% to 2% of all primary lung tumors.[1–3] Usually no obvious clinic features can be observed at early stage and paarneoplastic syndromes are really infrequent manifestation of neuroendocrine tumors, such as Cushing syndrome, Raynaud phenomenon, and Guillain-Barre-like syndrome.[11,12] It is hard to make an exact diagnosis of such disease. So far, there are no ideal tumor markers and lab index of TPC. On the CT scan, early TPC usually represent as a solitary nodule and sometimes it may have a lobulated appearance.[1] However, it also lacks of specificity image manifestations and sometimes it may be difficult to distinguish it from other space occupying lesions. It is reported 18F-FDG PET-CT may be effective in early diagnosis of TPC, but this issue is controversial at present.[13] However, in our case, the ectopic source was located in middle lobe of right lung and it is quite difficult to distinguish with other pulmonary nodules on CT scan, such as intrapulmonary lymph nodes. The character of the nodule was defined by FDG PET-CT.

Due to our patient's good physical condition, a surgical resection, which allows complete remission in about 83% of patients with a single primary lesion, was the preferred treatment strategy for him and limited pulmonary resection is performed by enucleation or wedge resection, when possible by video-assisted thoracic surgery.[4,14]

Although cases of Cushing syndrome secondary to TPC have been reported, detailed information on the genetic changes is not available. In our case, the tumor showed a mutation (S1240Cfs*21) in BCOR gene. BCOR gene can coding the transcription corepressor of BCL6 gene, which can impact cell apoptosis through specific interaction with the POX virus and zinc finger domain of BCL6 gene.[15] S1240Cfs means a flame shifting change with Serine1240 and it turns to be Cysteine. It may stop gene encoding at the 21th codon codes, making the mRNA degrading and expression depletion. Although have not been reported in TPC before, mutations besides BCOR S1240Cfs have been reported in other neuroendocrine tumors.[16] What's more, with the development and popularization of gene sequencing, BCOR gene alterations have been detected wildly in pulmonary neuroendocrine tumor (Fig. 4), but it has never been reported in Cushing syndrome secondary to TPC.[17–19] So far, targeted therapy of TPC is in groping stage. Somatostatin analogs have been widely used to control hormone excess symptoms. Cushing syndrome can be treated with ketoconazole, metyrapone, etomidate, or mifepristone.[6] However, no targeted drugs have been proven effective in treating TPC with expression of BCOR and other special surface receptors. Tiberi et al[20] identify BCL6, a transcriptional repressor and lymphoma oncoprotein, is a pivotal factor required for neurogenesis and tumor suppression of medulloblastoma. This study proves BCL6/BCOR/SIRT1 complex as a potent repressor of the Sonic Hedgehog pathway (SHH) in normal and oncogenic neural development, with direct diagnostic and/or therapeutic relevance for SHH medulloblastoma. For the time being, targeted therapy for TPC is still in groping stage and this issue needs further research.

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