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Case Report

Small Cell Lung Cancer with Dual Paraneoplastic Syndromes: A Case Report

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Keywords
Small cell lung cancer · Paraneoplastic syndrome · Ectopic adrenocorticotropic hormone syndrome · Amylase · Serum lipase · Lactate dehydrogenase

Abstract
Introduction: Paraneoplastic syndromes are common in cancers such as lung, breast, and ovarian cancers. Still, the dual paraneoplastic syndromes of ectopic adrenocorticotropic hormone (ACTH) syndrome (EAS) and raised pancreatic enzymes at the same time are rare. EAS is due to the production of ACTH by tumors other than the pituitary gland, which stimulates the hyperplasia of the adrenal cortex to secrete excessive corticosteroids, most commonly in lung cancer. Elevated pancreatic enzymes are associated with ectopic secretion from lung cancer. Clinically, some patients with small cell lung cancer (SCLC) have atypical early clinical manifestations and may present with paraneoplastic syndrome as the first symptom. ***Case Report:*** This article describes a case of a 45-year-old male patient who was admitted to the hospital with "intermittent mild edema of both lower extremities for more than 1 month" and showed persistent low potassium without diuretic drugs and with abnormally high blood amylase and blood lipase in the exclusion of pancreatitis. The persistent low potassium was caused by unusually high cortisol levels in patients with EAS that result from large amounts of cortisol secretion. Pancreatitis was excluded, and he was finally diagnosed with extensive-stage SCLC after bronchoscopic biopsy and histopathological confirmation. The patient presented with dual paraneoplastic syndromes of SCLC combined with EAS, high pancreatic enzymes, dual metastases, high malignancy, loss of surgical opportunities, and poor prognosis. The patient died at the end of the first cycle of chemotherapy due to the combination of IV degree of myelosuppression, metabolic alkalosis, severe infection, respiratory failure, and the rapid deterioration of his condition. ***Conclusion:*** Most of the clinical manifestations of lung cancer with paraneoplastic syndrome as the first symptom lack specificity. The paraneoplastic

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syndrome of lung cancer can appear in all stages of the disease, and if it appears before the diagnosis of lung cancer, it is of some significance in guiding the diagnosis of lung cancer. Meanwhile, when pancreatic lesions are excluded, we should consider malignancy-related hyperpancreatinemia.

Introduction

Paraneoplastic syndrome is a systemic disease caused by the abnormal immune response of tumor products or other unknown causes. It is not linked to the original tumor or its metastases; rather, it is caused by the tumor's products (hormones, cytokines, peptides, growth factors, etc.) or an abnormal immune response (including immune complex deposition, autoimmunity, and cross-immunity) or by other unexplained causes. These can lead to problems with the endocrine, digestive, neurological, hematopoietic, bone, joint, kidney, skin, and other systems. It is both a metabolic aberration brought on by release factors secreted by tumors and an autoimmunity-mediated condition [1]. According to reports, paraneoplastic syndromes account for 10%–15% of cancer cases. These syndromes are the second leading cause of death for cancer patients, after the actual illness [2].

Small cell lung cancer (SCLC) is a neuroendocrine tumor characterized by rapid progression and early and extensive metastasis, accounting for about 15%–20% of all lung cancers, but about 70% of patients with SCLC are in the extensive stage at the time of diagnosis [3], with rapid value-added and early widespread metastasis. Its neuroendocrine granules can secrete hormones and enzymes, causing paraneoplastic syndrome. Two or more paraneoplastic endocrine syndromes may coexist in patients with SCLC.

Adrenocorticotropic hormone (ACTH) secretion was the first paraneoplastic endocrine syndrome described in the literature, with the most common tumors being SCLC. In addition, the first case report of elevated serum amylase due to lung cancer was published in 1951, suggesting that the incidence of elevated serum amylase is more common in men and is associated with a poorer prognosis [4]. We herein report a rare case involving a patient with SCLC who exhibited dual paraneoplastic syndromes as the first symptoms (ectopic ACTH syndrome [EAS] and elevated pancreatic enzymes).

Case Description

History of Present Illness

A 45-year-old Chinese man was admitted to the Department of Endocrinology of our hospital on 27 January 2023 with a >1-month history of intermittent bilateral lower limb edema. More than 1 month before presentation to our institution, the patient developed intermittent sunken edema of the bilateral lower extremities with generalized weakness, and examination revealed severe hypokalemia (1.95 mmol/L). He was treated with potassium chloride extended-release tablets for potassium supplementation. However, the treatment effect was poor and the symptoms recurred. Four days before admission, at which time he had a random blood glucose concentration of 11.9 mmol/L, potassium concentration of 2.30 mmol/L, LDH concentration of 982.4 U/L, and α-hydroxybutyrate dehydrogenase (α-HBDH) concentration of 593.9 U/L.

Case Rep Oncol 2025;18:159–168
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History of Past Illness

He had a 6-month history of arterial hypertension and a 2-month history of diabetes mellitus; had smoked cigarettes; had drunk alcohol for the last 20 years; had a history of hypertension for 6 months, blood pressure up to 180/110 mm Hg, not treated with antihypertensive medication, no blood pressure testing; and had a history of previous diabetes mellitus for 2 months (details unknown); he had denied history of coronary heart disease, cerebral infarction, hepatitis, tuberculosis, and other infectious diseases and their close contact, and cortisol drug use.

Physical Examination

Physical examination revealed a body temperature of 36.5°C, pulse of 86 beats/min, respiratory rate of 20 breaths/min, blood pressure of 166/116 mm Hg, height of 171 cm, weight of 60 kg, and body mass index of 20.52 kg/m^2. He had mild edema of the face and eyelids as well as mild sunken edema of both lower limbs; the rest of the physical examination revealed no abnormalities.

The Laboratory Tests Revealed the Following

Blood tests revealed leukocytosis (12.08 × 10^9/L) (normal 3.5–9.5 × 10^9/L) and neutrophilia (11.06 × 10^9/L) (normal 1.8–6.3 × 10^9/L): glycated hemoglobin, 6.80% (normal 4.0–6.1%); urine glucose, 2+; and fasting blood glucose, 7.34 mmol/L (normal 3.9–6.1 mmol/L). An insulin C-peptide release test at 0 h (fasting) showed a C-peptide concentration of 0.49 nmol/L (normal 0.21–0.91 nmol/L) and insulin concentration of 44.13 pmol/L (normal 13–161 pmol/L). Arterial blood gas analysis showed metabolic alkalosis: pH, 7.55; $PaCO_2$, 37.0 mm Hg (normal 35.0–45.0 mm Hg); serum bicarbonate 31.6 mmol/L (normal 22.0–29.0 mmol/L); sodium concentration, 145. 8 mmol/L (normal 137.0–145.0 mmol/L); potassium concentration, 2.0 mmol/L (normal 3.5–5.3 mmol/L); chlorine concentration, 92.9 mmol/L (normal 99.0–110.0 mmol/L); serum amylase, 3,576.1 U/L (normal 35.0–135.0 U/L); lipase, 97.5 U/L (normal 5.0–55.0 U/L); LDH, 994.6 U/L (normal 109.0–245.0 U/L); and α-HBDH 538.7 U/L (normal 59.0–126.4 U/L). His NT-proBNP concentration was 498.6 pg/mL (normal 15.0–125.0 nmol/L), and his tumor markers were as follows: carcinoembryonic antigen (CEA), 10.32 ng/mL (normal 0–5 ng/mL); carbohydrate antigen 199 (CA199), 28.7 U/mL (normal 0–25 U/mL); neuron-specific enolase (NSE), 173.00 μg/L (normal <16.3 μg/L); cytokeratin fragment 19 (CF211), 18.92 ng/mL (normal 0–3.5 ng/mL); and progastrin-releasing peptide (ProGRP) 4,546.99 pg/mL (normal 2–50 pg/mL) (Table 2). Endocrine laboratory examination (Table 1): endocrine laboratory tests showed that his COR concentration at 08:00, 16:00, and 00:00 was >1,704.97, >1,704.97, and >1,704.97 nmol/L, respectively, and that his ACTH concentration was 164.00, 155.00, and 148.00 pmol/L, respectively. His ACTH and COR levels were elevated, his circadian rhythms were lost, and COR secretion was not suppressed with the low-dose (1 mg at midnight) and high-dose (8 mg) dexamethasone tests. The patient's renin (recumbent) activity was 0.10 ng/mL/h (normal 0.15–2.33 ng/mL/h), renin (standing) activity was 0.10 ng/mL/h (normal 0.10–6.56 ng/mL/h), aldosterone (recumbent) activity was 59.80 pg/mL (normal 30–160 pg/mL), and aldosterone (standing) activity was 53.20 pg/mL (normal 70–300 pg/mL).

Imaging Examination

Magnetic resonance imaging of the pituitary gland showed no significant abnormalities. Enhanced computed tomography (CT) of the chest showed a soft tissue focus in the right hilar-inferior lobe of the lung with irregular morphology, uneven density, and a maximum cross-section of approximately 5.4 × 7.3 cm; enlarged lymph nodes were also seen in the

Table 1. Endocrine laboratory data

	8:00	16:00	0:00	1 mg-DST	HDDST
ACTH, pmol/L	164.00	155.00	148.00	153.00	221.00
Cortisol, nmol/L	>1,704.97	>1,704.97	>1,704.97	>1,704.97	>1,704.97

1 mg-DST, 1 mg dexamethasone suppression test; HDDST, high-dose dexamethasone suppression tests.

Table 2. Laboratory data

	At admission	First cycle of chemotherapy ends	Normal range
HbA1c, %	6.8	6.9	(4.0–6.1)
Urine glucose	2+	–	(–)
Glucose, mmol/L	7.34	5.94	(3.9–6.1)
C-peptide, nmol/L	0.49	–	(0.21–0.91)
Insulin, pmol/L	44.13	–	(13–161)
pH	7.55	7.57	(7.35–7.45)
PaCO2	37	38	(35–45)
HCO3	31.6	33.2	(22.0–29.0)
Sodium, mmol/L	145.8	143.8	(137.0–145.0)
Potassium, mmol/L	2.0	2.4	(3.5–5.3)
Chloride, mmol/L	92.9	94.2	(99.0–110.0)
S-amy, U/L	3,576.1	1,872.3	(35.0–135.0)
Lipase, U/L	97.5	45.0	(5.0–55.0)
LDH, U/L	994.6	761.4	(109.0–245.0)
α-HBDH, U/L	538.7	416.4	(59.0–126.4)
NT-proBNP, pg/mL	498.60	383.26	(15.00–125.00)

S-amy, serum amylase; LDH, lactate dehydrogenase; α-HBDH, α-hydroxybutyrate dehydrogenase; HbA1c, hemoglobin A1c; NT-proBNP, N-terminal pro-brain natriuretic peptide; ACR, albumin-to-creatinine ratio.

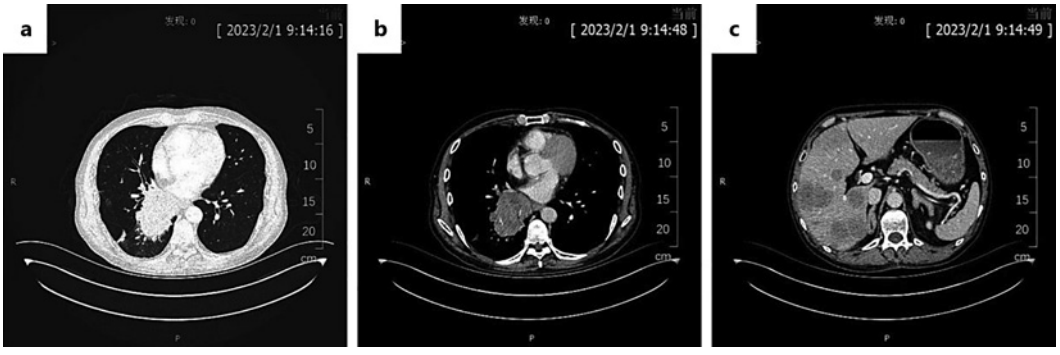

Fig. 1. a, **b** Contrast-enhanced chest CT showed soft tissue foci in the right hilar-inferior lobe and enlarged lymph nodes in the mediastinum, distal obstructive pneumonia, and right-sided pleural effusion. **c** Abdominal CT showed multiple liver metastases, bilateral adrenal metastases, and a normal pancreas.

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mediastinum, distal obstructive pneumonia, and right-sided pleural effusion (Fig. 1a, b). A CT scan of the abdomen showed bilateral adrenal thickening, possible metastasis, and liver metastasis; pancreatic lesions were excluded (Fig. 1c). These findings in combination with the markedly elevated tumor markers were highly suggestive of a lung tumor. Whole-body bone imaging showed no significant abnormalities. Tracheoscopic pathology suggested small cell carcinoma (Fig. 2a). Immunohistochemical examination revealed the following: CD56 (+) (Fig. 2b), CgA (+) (Fig. 2c), Syn (+) (Fig. 2d), Ki-67 (+80%), and ACTH (−).

Diagnosis and Treatment

The patient was given oral potassium chloride potassium supplementation treatment, but the effect was not good, given intravenous potassium chloride drip treatment, the patient's blood potassium elevation was not obvious. The patient's blood pressure was high, oral antihypertensive drug treatment was given, the patient's blood sugar was high, and intermittent hypoglycemic treatment was given. Based on our patient's clinical manifestations, markedly elevated COR and ACTH concentrations with loss of circadian rhythms, and lack of suppression by a low dose of dexamethasone, the first diagnosis we considered was ACTH-dependent Cushing's syndrome, which may be caused by Cushing's disease (CD) or another tumor. To further exclude CD and to clarify the diagnosis, therefore, the pituitary MR was perfected. Pituitary magnetic resonance imaging showed no significant abnormalities, and no suppression was seen on the high-dose dexamethasone test; thus, the diagnosis of EAS was then considered. We further performed intensive CT of the chest showing a soft tissue focus in the right hilar-inferior lobe of the lung; bronchoscopic biopsy pathology suggested small cell carcinoma, and immunohistochemical examination revealed the following: Syn (+), CgA (+), CD56 (+) were consistent with neuroendocrine tumors. However, the negative ACTH immunohistochemistry could have been attributed to the heterogeneous sampling of the tumor (the patient's specimen was an in vivo biopsy rather than a postoperative pathological section) and the very rapid metabolism of ACTH [5–7]. In addition, some research has revealed that the ACTH secreted by the tumor differs from the normal structure of ACTH, and the presence of ectopic ACTH secretion in the tumor cannot be diagnosed by the immunohistochemistry method, which detects the ACTH of the primary or metastatic tumor specimen. Therefore, the following diagnoses were considered: SCLC of the right lung (extensive stage) and EAS. The recommended first-line treatment option according to treatment guidelines is chemotherapy combined with immunochemotherapy, but this patient had a PS score of 4, and chemotherapy was recommended. After the exclusion of relevant contraindications, chemotherapy was administered using the EP regimen (etoposide 0.1 g on days 1–5, cisplatin 40 mg on days 1–3). At the end of the first cycle of chemotherapy, repeat laboratory tests showed an ACTH concentration of 119.00 pmol/L, blood amylase of 1,872.30 U/L, and LDH of 761.4 U/L (lower than at the time of diagnosis, but still higher than normal); COR concentration of >1,704.97 nmol/L (no change); and persistent refractory hypokalemia (which was considered to be related to the primary tumor). The patient's condition dramatically deteriorated, and he died of a combination of myelosuppression, metabolic alkalosis, severe infection, and respiratory failure at the end of the first cycle of chemotherapy.

Discussion

Although the association between Cushing's syndrome and nonpituitary tumors was originally documented in 1928, it was not until 1962 that the connection between the disease and ectopic corticosteroid secretion was established [8]. Cushing's syndrome is a general term for conditions caused by excessive secretion of glucocorticoids (mainly COR) by the adrenal glands of various etiologies. Approximately 85%–90% of such cases are ACTH-dependent

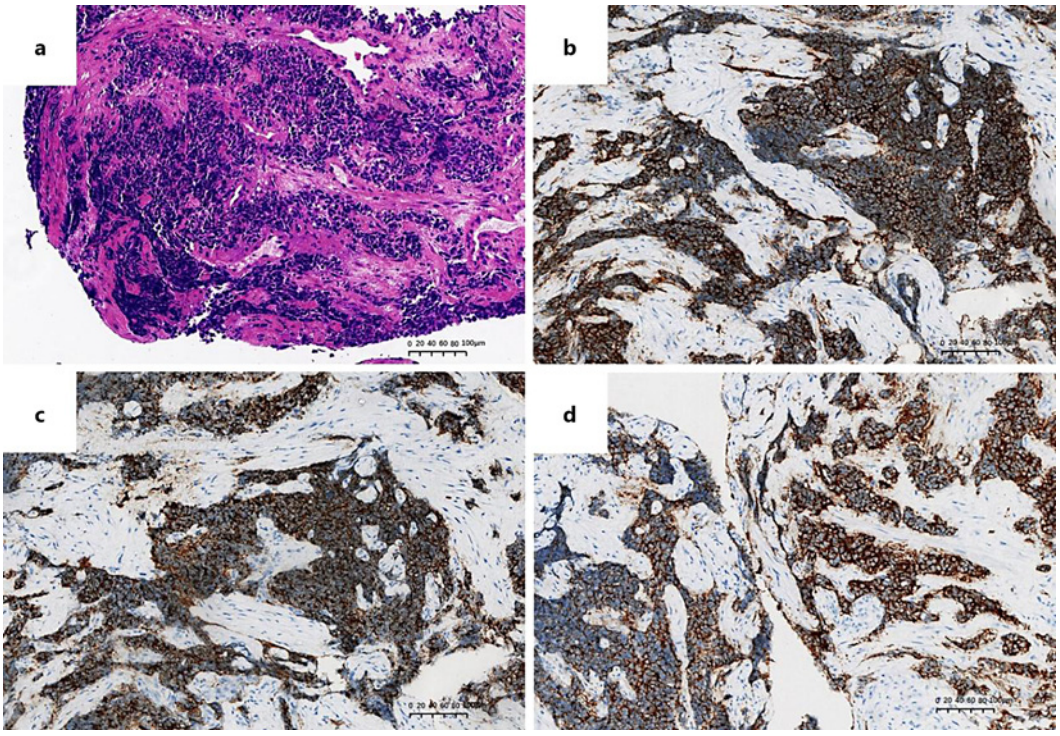

Fig. 2. a Histopathologic examination of a lung biopsy specimen (hematoxylin-eosin staining) showed SCLC. **b** CD56 staining of the tissue. **c** CgA staining of the tissue. **d** Syn staining of the tissue.

Cushing's syndrome. The most common cause of such Cushing's syndrome is pituitary ACTH hypersecretion (CD); the remaining 5%–15% of cases are secondary to abnormal ectopic secretion of ACTH and/or CRH by tumor cells, most of which involve ectopic secretion of ACTH by tumor cells (EAS) [9]. EAS refers to a series of symptoms caused by the secretion of a large amount of ACTH by tissues other than the pituitary gland, which stimulates the hyperplasia of the adrenal cortex and causes it to secrete excessive COR, mineralocorticoids, and sex hormones. Clinically, it can be divided into slow-progressing and rapidly progressive [10], the clinical manifestations and laboratory tests of the slow-developing type are similar to CD, and the rapidly progressive type is severe, often lacking the manifestations of typical Cushing's syndrome, mainly manifested as weight loss, hypertension, hyperglycemia, severe hypokalemia and edema. Combined with the clinical manifestations and related ancillary examinations of this patient, it is consistent with the rapidly progressive type.

The presentation of refractory hypokalemia, metabolic alkalosis, poor blood pressure control, and edema in this patient can be explained by the sodium-retaining effect of COR. Studies have found that 11β-hydroxysteroid dehydrogenase is adjacent to mineralocorticoid receptors, distributed in mineralocorticoid response tissues, and is adjacent to mineralocorticoid receptors. An abnormally elevated COR concentration in patients with EAS inactivates super type 2 11β-hydroxysteroid dehydrogenase (11βD-HSD2), and excess COR binds to mineralocorticoid receptors in the kidney, causing fluid retention, hypertension, hypokalemia, and metabolic alkalosis [11, 12]. There is a correlation between diabetes and insulin resistance and cancer development, with 8%–18% of people with diabetes having diabetes, and people with type 2 diabetes are 20%–30% more likely to die from cancer than people without diabetes. The fundamental mechanisms linking cancer to diabetes are long-term insulin resistance and hyperinsulinemia [13]. With respect to concurrent SCLC and abnormal glucose metabolism, we

believe that high concentrations of COR caused by ectopic ACTH may cause abnormal glucose metabolism through the following pathways [14]: COR accelerates hepatic gluconeogenesis by upregulating key enzymes of gluconeogenesis and inducing insulin resistance, thereby hindering the inhibitory effect of insulin on hepatic glucose output, increasing hepatic glucose output, and promoting hepatic lipid accumulation. In skeletal muscle, COR exacerbates insulin resistance by promoting ectopic fat deposition. In adipose tissue, COR promotes peripheral insulin resistance and diabetes by redistributing adipose tissue, increasing visceral adipose tissue, and increasing lipolysis, leading to abnormal secretion of adipogenic factors. In addition, COR inhibits insulin secretion in β cells, making it difficult to control blood sugar elevations. Eighty percent of patients with hypercortisolism have elevated blood pressure, usually persistent, with moderate or higher elevations in systolic and diastolic blood pressure. Hypercortisolism causes hypertension by the following mechanism [15]: High concentrations of COR can cause sodium and water retention in the body and increase circulating blood volume. High concentrations of COR are often accompanied by hypersecretion of mineralocorticoids, which enhance renal sodium reabsorption and increase blood volume. High concentrations of COR can inhibit the vasodilator system. High concentrations of COR can enhance the activity of plasma renin and activate the renin-angiotensin-aldosterone system. High concentrations of COR can increase the sensitivity of blood vessels to catecholamines and inhibit the breakdown of catecholamines. High concentrations of COR promote vasopressin release by increasing sympathetic nervous system activity.

Our patient presented with elevated blood amylase, α-HBDH, and lipase concentrations, but acute pancreatitis was excluded. Studies have shown that many malignancies can also cause an elevated blood amylase concentration, especially pancreatic, breast, lung, and ovarian cancers [16], and the blood amylase could be significantly reduced after effective treatment; this was most likely associated with ectopic secretion by lung cancer [17]. Some studies have shown that elevated amylase can be considered a manifestation of paraneoplastic syndrome in SCLC and that blood amylase can be used as a marker of treatment efficacy and prognosis [18]. In addition, some neuroendocrine tumors can produce large amounts of lipase. To date, cases have been reported in which lipase was elevated in patients with SCLC, and the enzyme level decreased after chemotherapy; in these cases, lipase could be used as a marker of treatment efficacy [17, 19]. Elevated lipase is an unusual paraneoplastic syndrome.

SCLC is a highly aggressive subtype of lung cancer with a particularly poor prognosis. Ectopic Cushing's syndrome, hypercortisolism due to ectopic hormone secretion, is estimated to account for 5%–15% of all cases of Cushing's syndrome (3–5). In addition, SCLC patients with comorbid paraneoplastic Cushing's syndrome (PCS) have a smaller percentage but a worse prognosis than all SCLC patients. Retrospective studies have shown that the median survival of SCLC patients with combined PCS is less than 7 months [20]. The longest survival reported by Sakuraba et al. was 117 months [21].

Current research suggests that there are two main aspects of treatment for patients with SCLC combined with PCS. On the one hand, controlling hypercortisolism and taking preventive measures against infection are crucial. Infection due to glucocorticoid-induced immunosuppression and chemotherapy-induced granulocyte deficiency is an important factor in the poor prognosis of patients with SCLC combined with PCS. According to relevant reports, the main therapeutic approaches to control hypercortisolism are steroidogenesis inhibitors [22, 23]. On the other hand, regarding the treatment of SCLC, the ultimate cause of hypercortisolism is the secretion of ectopic hormones by tumor tissues; therefore, the treatment of the primary tumor is the basis for the control of hypercortisolism, and effective anticancer treatments can alleviate the symptoms of PCS. This includes resection of the primary tumor, radiotherapy chemotherapy, etc. For EAS that cannot be debulked, drugs that inhibit cortisol synthesis (e.g., ketoconazole), glucocorticoid receptor antagonists (e.g., mifepristone), and inhibition of ACTH secretion (e.g., pareptiline) can be used. For

extensive-stage SCLC, chemotherapy is the basis of treatment, but the latest guidelines emphasize the important role of immunosuppression in the extensive stage, with the first-line treatment regimen being chemotherapy in combination with immunochemotherapy, combining cisplatin/etoposide with an immune checkpoint inhibitor (e.g., natalizumab or ibalizumab), and the addition of immunosuppressants has been shown to significantly prolong survival of patients [24]. The prognosis of patients with lung cancer and ectopic ACTH progresses rapidly and is related to a variety of factors, including age, clinical stage, histologic type, and serum COR levels [25, 26], and the vast majority of patients have lost the best chance of surgical treatment at the time of diagnosis, and the mortality rate is high even with chemotherapy [8].

Conclusions

Since PCS is a marker of poor prognosis in SCLC patients, early differential diagnosis of PCS is essential to assess the prognosis of SCLC patients. The key is to differentiate ectopic Cushing's syndrome from CD, and it is crucial for clinicians to raise awareness of paraneoplastic syndromes and to achieve early diagnosis and treatment, which is essential for the prognosis of patients. It is expected that there will be high-quality studies in the future to evaluate the efficacy and safety of new therapeutic approaches regarding SCLC, especially immunotherapy, in the future treatment of SCLC.

Statement of Ethics

This study protocol was reviewed and approved by the Scientific Research Ethics Committee of the First People's Hospital of Jining City, Approval No. JNRM-2024-KY-039. All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional and/or National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study obtained written informed consent for publication from the patient's family. According to legal or medical authorities, the patient's family member has been designated as the legal guardian and is permitted to provide consent on behalf of the patient. The CARE Checklist has been completed by the authors for this case report, attached as online supplementary material (for all online suppl. material, see https://doi.org/10.1159/000542763).

Conflict of Interest Statement

The authors declare no conflict of interest.

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Author Contributions

Conceptualization, investigation, and writing: Jingjing Song. Resources and Supervision: Linlin Fan.

Data Availability Statement

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request.

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