Long-term Survival of a Patient with Small Cell Lung Cancer Secreting ADH and ACTH Simultaneously, Following the Prolonged Use of Amrubicin: A Case Report

Aya Kosuda¹, Toru Shirahata², Nasa Kudo¹, Yuki Uehara¹, Masayoshi Miyawaki³, Aika Hagiwara³, Rie Murakami³ and Ken Shimizu⁴

Abstract:
Paraneoplastic syndromes are frequently observed in lung cancer, especially in small cell lung cancer (SCLC). Although there have been many reports on paraneoplastic syndromes, few reports have been published on SCLC that simultaneously produces antidiuretic hormone (ADH) and adrenocorticotropic hormone (ACTH), and these reports described the prognosis of such cases as extremely poor. We herein present a rare case of a Japanese woman with SCLC accompanied by syndrome of inappropriate secretion of antidiuretic hormone (SIADH) and Cushing’s syndrome. The survival of the patient was prolonged by the long-term administration of amrubicin.

Key words: small cell lung cancer, SIADH, Cushing syndrome, FDG-PET, somatostatin receptor scintigraphy, amrubicin

Introduction
Small cell lung cancer (SCLC) is a tumor characterized by differentiation into the neuroendocrine system and the secretion of various types of hormones, including antidiuretic hormone (ADH), adrenocorticotropic hormone (ACTH), serotonin, and calcitonin. These hormones lead to the development of paraneoplastic syndromes, and sometimes symptoms such as consciousness disturbance or weakness precede other clinical features of the cancer.

Syndrome of inappropriate secretion of antidiuretic hormone (SIADH) is a disorder of water balance characterized by hypotonic hyponatremia, concentrated urine, and a euolemic state, caused by the inability to suppress ADH secretion. There are many causes of SIADH, including malignancy, pulmonary disease, medications, and any disorder involving the central nervous system that disrupts the ability to regulate vasopressin secretion. Previous studies have shown that SIADH affects 1-2% of all cancer patients, most of whom have SCLC, with approximately 10-45% of all patients with SCLC developing SIADH (1). The diagnosis is established based on a clinical euolemic state with low serum sodium and osmolality, high urine sodium and osmolality, and the exclusion of pseudohyponatremia and diuretic use.

Paraneoplastic Cushing’s syndrome results from the ectopic production of ACTH and affects 1-5% of all patients diagnosed with Cushing’s syndrome (2); approximately 50-60% of these cases are neuroendocrine lung tumors (carcinoid tumors [30-46%]; SCLC [8-20%]) (3-5). The diagnosis is established under high clinical suspicion based on elevated cortisol and ACTH levels in addition to a positive dexamethasone suppression test.

It is noteworthy that thus far, there have been only nine reported cases wherein SCLC produced these two hormones

¹Department of General Internal Medicine, JCHO Saitama Medical Center, Japan, ²Department of Respirology, JCHO Saitama Medical Center, Japan, ³Department of Endocrinology, Metabolism, and Nephrology, JCHO Saitama Medical Center, Japan and ⁴Department of Diagnostic Pathology, JCHO Saitama Medical Center, Japan
Received: February 15, 2019; Accepted: July 29, 2019; Advance Publication by J-STAGE: September 11, 2019
Correspondence to Dr. Toru Shirahata, t.shirahata+doctor@gmail.com
simultaneously (2, 6-13). According to these reports, the opposing effects of cortisol and ADH on renal sodium excretion sometimes complicate the diagnosis or result in a misdiagnosis. In addition, the presence of these paraneoplastic syndromes is indicative of a poor prognosis in SCLC patients, with overall survival of only 2-4 months (2, 6-9, 13).

The present report describes the clinical and imaging characteristics of SCLC with paraneoplastic endocrinopathies, as well as the possibility of long-term survival following the prolonged use of amrubicin (AMR), which is a key drug for treating SCLC.

**Case Report**

A 70-year-old woman was admitted to a nearby hospital in October 2015 because of headache and generalized fatigue in the two months prior to her presentation. Her past medical history included spinal canal stenosis and lumbar compression fracture due to osteoporosis, and she had a family medical history of diabetes mellitus. She had a 40-pack-year history of smoking. The first blood test showed hyponatremia (126 mEq/L [normal range: 135-145]). A doctor in the hospital first diagnosed the patient with mineralocorticoid responsive hyponatremia of the elderly and prescribed fludrocortisone. However, her symptoms and hyponatremia did not improve, and over the next 2 months, she gained 3 kg in body weight. Thus, she visited our hospital for further investigation.

On admission, her status was as follows: consciousness, clear; height, 153 cm; body weight, 45 kg; body mass index, 19.2 (kg/m²); body temperature, 36.3°C; blood pressure, 132/93 mmHg; pulse, 67 beats/min and regular; and SpO₂, 99% (room air). Her cardiac and breathing sounds were clear, and neither palpable lymph nodes nor abdominal hepatosplenomegaly was observed. She had pitting edema of both lower limbs, central obesity, and buffalo hump. Blood testing revealed the following findings: hyponatremia (sodium level, 129 mEq/L [normal range: 135-145]); hypokalemia (potassium level, 2.4 mEq/L [normal range: 3.5-5.1]); serum osmolality, 267 mOsm/kg (normal range: 275-295 mOsm/kg); serum uric acid, 1.8 mg/dL (normal range: 2.5-7.0 mg/dL); serum ADH, 1.0 pg/mL; urinary sodium, 174 mmol/L (normal range: 40-220 mmol/L); and urine osmolality, 633 mOsm/kg (normal range: 300-900 mOsm/kg). These values were consistent with a diagnosis of SIADH.

Cushing’s syndrome was suspected based on the patient’s clinical presentation (hypokalemia, osteoporosis, and appearance); thus, the serum ACTH and cortisol levels were measured and found to be 253 pg/mL (normal range: 0-46 pg/mL) and 30.3 μg/dL (normal range: 10-20 μg/dL), respectively. A suppression test using dexamethasone (0.5 mg) demonstrated that the cortisol level did not decrease (cortisol and ACTH were 47.1 μg/dL and 293 pg/mL, respectively). On the second day, the 24-h urine free cortisol level was 2,280 μg/24 hours (normal range: 4.3-176). The administration of dexamethasone (8 mg) failed to suppress her cortisol level (cortisol and ACTH were 48.4 μg/dL and 273 pg/mL, respectively). In a CRH loading test, the patient’s plasma ACTH did not respond for the duration of the test. Brain (including the pituitary gland) magnetic resonance imaging (MRI) confirmed the absence of any pituitary abnormalities. SIADH and ectopic Cushing’s syndrome were diagnosed based on the results of these extensive investigations. Contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis revealed a mass on the upper lobe of the right lung and enlargement of the right hilar and mediastinal lymph nodes (Fig. 1A-C). No metastases were observed in any other sites of the body. The patient underwent transbronchial lung biopsy, and the pathological findings revealed SCLC, with positive staining of chromogranin A and synaptophysin. The stage was cT2aN3M0 (8th edition of the TNM classification), which was considered to be limited disease.

At first, hyponatremia was treated with fluid restriction, but because of refractory hyponatremia and hypokalemia, alactone and tolvaptan were prescribed. Cisplatin and VP-16 combination chemotherapy was also initiated, accompanied by accelerated hyperfractionated thoracic radiotherapy at a high dose of 45 Gy for the lung cancer, which resulted in a reduction of the tumor and an improvement in the patient’s electrolyte levels. Thus, we subsequently planned to perform prophyllactic cranial irradiation, but follow-up brain MRI 2 months after the last chemotherapy treatment revealed brain metastases; thus, whole brain irradiation (WBR) was performed with a dose of 30 Gy.

At three months after WBR, CT revealed bilateral adrenal metastases (Fig. 2), and blood testing showed the recurrence of hyponatremia (128 mEq/L) but no hypokalemia (4.5 mEq/L). She was hospitalized because of nausea and muscle weakness. After her hyponatremia improved following the injection of 3% saline, AMR (40 mg/m²) was administered for 3 consecutive days at certain time intervals, according to her condition, as a second-line treatment for relapsed SCLC; however, grade 4 neutropenia was observed according to the National Cancer Institute’s Common Toxicity Criteria for Adverse Events version 4.0. Thus, she was treated with an 80% dose of AMR with prophylactic pegylated granulocyte colony stimulating factor (Peg-G-CSF), which resulted in no particular side effects.

Although the adrenal glands remained slightly enlarged, no electrolyte abnormalities reappeared. She underwent stereotactic radiosurgery for brain metastasis several times during the course of AMR treatment. Ultimately, AMR was discontinued when the cumulative dose reached 1,022 mg/m² because her Eastern Cooperative Oncology Group performance status worsened to grade 3. No cardiac adverse effects were detected on chest radiography, electrocardiography, or echocardiography. At the time these tests were conducted, 2 years and 5 months had passed since AMR was first administered.

Furthermore, the blood levels of both ACTH and ADH increased (ACTH: 259 pg/mL, ADH: 12.4 pg/mL). To further
SCLC is an aggressive subtype of lung cancer that accounts for approximately 15% of all lung cancers and which mainly occurs in smokers. Most cases are characterized by rapid growth and are discovered with disseminated disease; however, they exhibit good initial sensitivity to chemotherapy and radiotherapy. SCLC is categorized into lung neuroendocrine tumors (NETs), which are classified into four subtypes: well-differentiated, low-grade typical carcinoids (TCs); well-differentiated, intermediate-grade typical carcinoids (ACs); poorly differentiated, high-grade large cell neuroendocrine carcinomas (LCNECs); and poorly differentiated, high-grade SCLCs. SCLCs and LCNECs are considered to be more aggressive (clinically and pathologically) than pulmonary carcinoids (14). In terms of histopathological features, positive immunostaining for chromogranin A, synaptophysin, and CD56 is believed to be indicative of SCLC. Besides, as the somatostatin receptor is also highly expressed in NET, SRS is thought to be a useful imaging technique because it enables the diagnosis of NETs and aids in the preparative treatment response to octreotide.

PET-CT is often used for the diagnosis of lung cancer; furthermore, SRS can visualize the primary SCLC tumor progression of cancer. In total, the patient received 9 cycles of amrubicin with a cumulative total dose of 1,350 mg.

Informed consent for the publication of this case report was obtained from the patient’s family.

**Discussion**

SCLC is an aggressive subtype of lung cancer that accounts for approximately 15% of all lung cancers and which mainly occurs in smokers. Most cases are characterized by rapid growth and are discovered with disseminated disease; however, they exhibit good initial sensitivity to chemotherapy and radiotherapy. SCLC is categorized into lung neuroendocrine tumors (NETs), which are classified into four subtypes: well-differentiated, low-grade typical carcinoids (TCs); well-differentiated, intermediate-grade typical carcinoids (ACs); poorly differentiated, high-grade large cell neuroendocrine carcinomas (LCNECs); and poorly differentiated, high-grade SCLCs. SCLCs and LCNECs are considered to be more aggressive (clinically and pathologically) than pulmonary carcinoids (14). In terms of histopathological features, positive immunostaining for chromogranin A, synaptophysin, and CD56 is believed to be indicative of SCLC. Besides, as the somatostatin receptor is also highly expressed in NET, SRS is thought to be a useful imaging technique because it enables the diagnosis of NETs and aids in the preparative treatment response to octreotide.

PET-CT is often used for the diagnosis of lung cancer; furthermore, SRS can visualize the primary SCLC tumor progression of cancer. In total, the patient received 9 cycles of amrubicin with a cumulative total dose of 1,350 mg.

Informed consent for the publication of this case report was obtained from the patient’s family.

**Discussion**

SCLC is an aggressive subtype of lung cancer that accounts for approximately 15% of all lung cancers and which mainly occurs in smokers. Most cases are characterized by rapid growth and are discovered with disseminated disease; however, they exhibit good initial sensitivity to chemotherapy and radiotherapy. SCLC is categorized into lung neuroendocrine tumors (NETs), which are classified into four subtypes: well-differentiated, low-grade typical carcinoids (TCs); well-differentiated, intermediate-grade typical carcinoids (ACs); poorly differentiated, high-grade large cell neuroendocrine carcinomas (LCNECs); and poorly differentiated, high-grade SCLCs. SCLCs and LCNECs are considered to be more aggressive (clinically and pathologically) than pulmonary carcinoids (14). In terms of histopathological features, positive immunostaining for chromogranin A, synaptophysin, and CD56 is believed to be indicative of SCLC. Besides, as the somatostatin receptor is also highly expressed in NET, SRS is thought to be a useful imaging technique because it enables the diagnosis of NETs and aids in the preparative treatment response to octreotide.

PET-CT is often used for the diagnosis of lung cancer; furthermore, SRS can visualize the primary SCLC tumor progression of cancer. In total, the patient received 9 cycles of amrubicin with a cumulative total dose of 1,350 mg.

Informed consent for the publication of this case report was obtained from the patient’s family.

**Discussion**

SCLC is an aggressive subtype of lung cancer that accounts for approximately 15% of all lung cancers and which mainly occurs in smokers. Most cases are characterized by rapid growth and are discovered with disseminated disease; however, they exhibit good initial sensitivity to chemotherapy and radiotherapy. SCLC is categorized into lung neuroendocrine tumors (NETs), which are classified into four subtypes: well-differentiated, low-grade typical carcinoids (TCs); well-differentiated, intermediate-grade typical carcinoids (ACs); poorly differentiated, high-grade large cell neuroendocrine carcinomas (LCNECs); and poorly differentiated, high-grade SCLCs. SCLCs and LCNECs are considered to be more aggressive (clinically and pathologically) than pulmonary carcinoids (14). In terms of histopathological features, positive immunostaining for chromogranin A, synaptophysin, and CD56 is believed to be indicative of SCLC. Besides, as the somatostatin receptor is also highly expressed in NET, SRS is thought to be a useful imaging technique because it enables the diagnosis of NETs and aids in the preparative treatment response to octreotide.

PET-CT is often used for the diagnosis of lung cancer; furthermore, SRS can visualize the primary SCLC tumor progression of cancer. In total, the patient received 9 cycles of amrubicin with a cumulative total dose of 1,350 mg.

Informed consent for the publication of this case report was obtained from the patient’s family.

**Discussion**

SCLC is an aggressive subtype of lung cancer that accounts for approximately 15% of all lung cancers and which mainly occurs in smokers. Most cases are characterized by rapid growth and are discovered with disseminated disease; however, they exhibit good initial sensitivity to chemotherapy and radiotherapy. SCLC is categorized into lung neuroendocrine tumors (NETs), which are classified into four subtypes: well-differentiated, low-grade typical carcinoids (TCs); well-differentiated, intermediate-grade typical carcinoids (ACs); poorly differentiated, high-grade large cell neuroendocrine carcinomas (LCNECs); and poorly differentiated, high-grade SCLCs. SCLCs and LCNECs are considered to be more aggressive (clinically and pathologically) than pulmonary carcinoids (14). In terms of histopathological features, positive immunostaining for chromogranin A, synaptophysin, and CD56 is believed to be indicative of SCLC. Besides, as the somatostatin receptor is also highly expressed in NET, SRS is thought to be a useful imaging technique because it enables the diagnosis of NETs and aids in the preparative treatment response to octreotide.

PET-CT is often used for the diagnosis of lung cancer; furthermore, SRS can visualize the primary SCLC tumor progression of cancer. In total, the patient received 9 cycles of amrubicin with a cumulative total dose of 1,350 mg.

Informed consent for the publication of this case report was obtained from the patient’s family.

**Discussion**

SCLC is an aggressive subtype of lung cancer that accounts for approximately 15% of all lung cancers and which mainly occurs in smokers. Most cases are characterized by rapid growth and are discovered with disseminated disease; however, they exhibit good initial sensitivity to chemotherapy and radiotherapy. SCLC is categorized into lung neuroendocrine tumors (NETs), which are classified into four subtypes: well-differentiated, low-grade typical carcinoids (TCs); well-differentiated, intermediate-grade typical carcinoids (ACs); poorly differentiated, high-grade large cell neuroendocrine carcinomas (LCNECs); and poorly differentiated, high-grade SCLCs. SCLCs and LCNECs are considered to be more aggressive (clinically and pathologically) than pulmonary carcinoids (14). In terms of histopathological features, positive immunostaining for chromogranin A, synaptophysin, and CD56 is believed to be indicative of SCLC. Besides, as the somatostatin receptor is also highly expressed in NET, SRS is thought to be a useful imaging technique because it enables the diagnosis of NETs and aids in the preparative treatment response to octreotide.

PET-CT is often used for the diagnosis of lung cancer; furthermore, SRS can visualize the primary SCLC tumor progression of cancer. In total, the patient received 9 cycles of amrubicin with a cumulative total dose of 1,350 mg.

Informed consent for the publication of this case report was obtained from the patient’s family.
Figure 3. Somatostatin receptor scintigraphy and positron emission tomography-computed tomography. (A) No abnormalities were seen on somatostatin receptor scintigraphy. (B) Positron emission tomography-computed tomography showed the avid uptake of fluorodeoxyglucose in the bilateral adrenal metastases.

Figure 4. Chemotherapy and radiotherapy as treatment of SCLC that simultaneously secreted adrenocorticotropic hormone (ACTH) and antidiuretic hormone (ADH), and the results of measurement of Na and progastrin-releasing peptide. WBR: Whole brain radiation

Table. Changes of the Arginine Vasopressin (AVP), Cortisol and ACTH Levels during Treatment.

|          | 2015/7 | 2016/9 | 2018/3 | 2018/5 | 2018/6 | 2018/7 | 2018/9 |
|----------|--------|--------|--------|--------|--------|--------|--------|
| AVP (pg/mL) | 1.0    |        |        |        |        |        |        |
| Cortisol (µg/dL) | 30.3  | 7.72   | 29.9   | 39.3   | 31.3   | 57.3   | 9.3    |
| ACTH (pg/mL)   | 253    | 253    | 259    | 329    | 503    | 503    | 154    |

with varying degrees of uptake in 63-100% of cases, whereas it can visualize regional and distant metastases in only 45-65% of cases (15). Although the administration of octreotide is not a standard therapy for SCLC, in a report,
octreotide in combination with antineoplastic agents showed a survival benefit in somatostatin receptor-positive patients (16) and peptide receptor radionuclide therapy (PRRT) might be a treatment option for patients exhibiting sufficient tracer uptake (17). Thus, an SRS examination may be beneficial in the treatment of SCLC. However, based on the negative SRS results, we did not use octreotide therapy.

As the accumulation of FDG was not observed in the primary tumor and was only found in adrenal metastases, ACTH and ADH were thought to have been produced by the metastatic lesions, and we confirmed that the serum ACTH and cortisol levels were improved by irradiation for adrenal metastasis. Thus, imaging studies were very useful in this case. With respect to the complementary role of FDG and SRS, it is possible that dual-tracer imaging is crucial for optimizing and personalizing therapeutic strategies according to the patient’s condition. Both examinations should be performed more frequently for NET patients in the future.

Previous reports described that patients with SCLC secreting both ACTH and ADH tend to have more extensive disease and are more likely to have a poor prognosis, with a survival time of 2-4 months after the diagnosis, because the disease is refractory to treatment. Although it is unclear why the survival time is so short, one possible reason may be the presence of hypercortisolism. Several studies using animal models have shown that steroids suppress the immune system and cause not only tumor growth but also metastatic development (18, 19). In breast cancer, patients who were treated with steroids had a significantly higher rate of metastasis in comparison to patients who did not receive steroids (20, 21). In addition, high cortisol levels attenuate the effect of cisplatin and carboplatin, which are key drugs for the treatment of SCLC (22). These studies indicate that SCLC develops aggressively under immunosuppressive circumstances caused by hypercortisolism. Furthermore, hypercortisolism has several negative effects: it causes serious infectious complications, as well as metabolic disorders such as hyperglycemia, hypokalemia, osteoporosis, and hypertension, which can significantly worsen the general health status.

AMR, a third-generation anthracycline and potent topoisomerase II inhibitor, has shown promising activity in many patients with SCLC (23-25). However, in addition to myelosuppression, myocardial disorders and congestive heart failure are well-known adverse reactions of anthracycline drugs. The frequency of cardiotoxicity increases when the anthracycline dose exceeds a certain level. For example, it has been suggested that the administration of >550 mg/m² of doxorubicin (DXR) should be avoided. When the total dose of DXR exceeds 550 mg, the rate of congestive heart failure reaches 26% (26). However, as far as AMR treatment is concerned, the threshold of irreversible myocardial injury is reportedly unclear, although arrhythmias and cardiac dysfunction are reported to occur in 1-5% cases (27). Thus, electrocardiography or echocardiography should be routinely performed to monitor the cardiac function.

In the present case, long-term-survival was achieved after long-term AMR chemotherapy. Despite the large total dose, severe cardiac adverse reactions were not observed, and a reduction in tumor markers and remission were confirmed. The benefit of long-term AMR chemotherapy for SCLC was previously discussed by Higashiguchi et al. (28), who reported that among 12 SCLC patients who received prolonged AMR chemotherapy as second-line therapy, the median cumulative dose of AMR was 2,076 mg (range = 1,200-2,856 mg), the mean number of cycles was 12 cycles (range = 8-20), and the median survival time was 1,104 days (range = 459-1,997 days). No patients experienced severe adverse effects.

Thus, the prolonged administration of AMR at a lower than recommended dose might exert antitumor effects with fewer side effects. Of course, there are few reports and further studies are required. Nevertheless, AMR may be a key drug that can be used as maintenance therapy for SCLC.

In conclusion, the prognosis of SCLC producing ADH and ACTH has been considered to be extremely poor, but there is a possibility of long-term survival with the use of AMR, as was observed in the present case. Prolonged lower-dose AMR therapy may be a treatment option for SCLC patients.

The authors state that they have no Conflict of Interest (COI).

References
1. Pelosof LC, Gerber DE. Paraneoplastic syndromes: an approach to diagnosis and treatment. Mayo Clinic proceedings 85: 838-854, 2010.
2. Agarwal KA, Soe MH. Beyond the Dual Paraneoplastic Syndromes of Small-Cell Lung Cancer with ADH and ACTH Secretion: A Case Report with Literature Review and Future Implications. Case reports in oncolodical medicine 2018: 4038397, 2018.
3. Issidori AM, Kaltasga GA, Pozza C, Frajese V, Newell-Price J, Reznek RH, et al. The ectopic adrenocorticotropin syndrome: clinical features, diagnosis, management, and long-term follow-up. J Clin Endocrinol Metab 91: 371-377, 2006.
4. Ilias I, Torpy DJ, Pack M, Mullen N, Greek RA, Nieman LK. Cushing’s syndrome due to ectopic corticotropin secretion: twenty years’ experience at the National Institutes of Health. J Clin Endocrinol Metab 90: 4955-4962, 2005.
5. Ghazi AA, Abbasi Dezfooli A, Amirbaigloo A, Daneshvar Kakhki A, Mohammadi F, Turgar F, et al. Ectopic Cushing’s syndrome secondary to lung and mediastinal tumours -- report from a tertiary care centre in Iran. Endokrynol Pol 66: 2-9, 2015.
6. Suzuki H, Tsutsui Y, Yamaguchi K, Abe K, Yokoyama T. Small cell lung carcinoma with ectopic adrenocorticotropic hormone and antidiuretic hormone syndromes: a case report. Japanese journal of clinical oncology 14: 129-137, 1984.
7. Shaker JL, Bricknell RC, Divgi AB, Raff H, Findling JW. Case report: renal phosphate wasting, syndrome of inappropriate antidiuretic hormone, and ectopic corticotropin production in small cell carcinoma. The American journal of the medical sciences 310: 38-41, 1995.
8. Pierce ST, Metcalfe M, Banks ER, O’Daniel ME, De Simone P. Small cell carcinoma with two paraneoplastic syndromes. Cancer 69: 2258-2261, 1992.
9. O’Neal LW, Kipnis DM, Luse SA, Lacy PE, Jarett L. Secretion of
various endocrine substances by ACTH-secreting tumors—gastrin, melanotropin, norepinephrine, serotonin, parathormone, vasopressin, glucagon. Cancer 21: 1219-1232, 1968.

10. Coscia M, Brown HD, Miller M, Tanaka K, Nicholson WE, Parks KR, et al. Ectopic production of antidiuretic hormone (adh), adrenocorticotropic hormone (ACTH) and beta-melanocyte stimulating hormone (beta-MSH) by an oat cell carcinoma of the lung. The American journal of medicine 62: 303-307, 1977.

11. Mayer S, Cypess AM, Kocher ON, Berman SM, Huberman MS, Hartzband P, et al. Uncommon presentations of some common malignancies: Case 1. Sequential paraneoplastic endocrine syndromes in small-cell lung cancer. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 23: 1312-1314, 2005.

12. Liddle GW, Givens JR, Nicholson WE, Island DP. The ectopic ACTH syndrome. Cancer research 25: 1057-1061, 1965.

13. Musig K, Horger M, Haring HU, Wehrmann M. Syndrome of in-appropriate antidiuretic hormone secretion and ectopic ACTH production in small cell lung carcinoma. Lung cancer (Amsterdam, Netherlands) 57: 120-122, 2007.

14. Hendifar AE, Marchevsky AM, Tuli R. Neuroendocrine Tumors of the Lung: Current Challenges and Advances in the Diagnosis and Management of Well-Differentiated Disease. Journal of thoracic oncology: official publication of the International Association for the Study of Lung Cancer 12: 425-436, 2017.

15. Reisinger I, Bohuslavitzki KH, Brenner W, Braune S, Dittrich I, Geide A, et al. Somatostatin receptor scintigraphy in small-cell lung cancer: results of a multicenter study. Journal of nuclear medicine: official publication, Society of Nuclear Medicine 39: 224-227, 1998.

16. Zarogoulidis K, Eleftheriadou E, Kontakiotis T, Gerasimou G, Zarogoulidis P, Sapardanis I, et al. Long acting somatostatin analogues in combination to antineoplastic agents in the treatment of small cell lung cancer patients. Lung cancer (Amsterdam, Netherlands) 76: 84-88, 2012.

17. Lapa C, Hanscheid H, Wild V, Pelzer T, Schirbel A, Werner RA, et al. Somatostatin receptor expression in small cell lung cancer as a prognostic marker and a target for peptide receptor radionuclide therapy. Oncotarget 7: 20033-20040, 2016.

18. Seshadri M, Poduval TB, Sundaram K, Studies on metastases. I. Role of sensitization and immunosuppression. Journal of the National Cancer Institute 63: 1205-1210, 1979.