Case-series of paraneoplastic Cushing syndrome in small-cell lung cancer

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Summary
The objective of this study is to report three cases of paraneoplastic or ectopic Cushing syndrome, which is a rare phenomenon of the adrenocorticotropic hormone (ACTH)-dependent Cushing syndrome. Three cases are reported in respect of clinical presentation, diagnosis and treatment in addition to relevant literature review. The results showed that ectopic ACTH secretion can be associated with different types of neoplasm most common of which are bronchial carcinoid tumors, which are slow-growing, well-differentiated neoplasms with a favorable prognosis and small-cell lung cancer, which are poorly differentiated tumors with a poor outcome. The latter is present in two out of three cases and in the remaining one, primary tumor could not be localized, representing a small fraction of patients with paraneoplastic Cushing. Diagnosis is established in the setting of high clinical suspicion by documenting an elevated cortisol level, ACTH and doing dexamethasone suppression test. Treatment options include management of the primary tumor by surgery and chemotherapy and treating Cushing syndrome. Prognosis is poor in SCLC. We concluded that in front of a high clinical suspicion, ectopic Cushing syndrome diagnosis should be considered, and identification of the primary tumor is essential.

Background
Cushing syndrome results from chronic exposure to excess glucocorticoids. Pituitary adenoma is the most common cause of adrenocorticotropic (ACTH)-dependent hypercortisolism. In a minority of patients, ACTH is secreted by an ectopic extrapituitary neuroendocrine tumor. Paraneoplastic Cushing syndrome is a diagnostic challenge. It can be associated with different types of tumors. Small-cell lung cancer (SCLC) and bronchial carcinoid tumors account for the majority of cases. Establishing the diagnosis is often difficult because few of symptoms and signs are pathognomonic. Moreover, tumors are usually difficult to localize, especially in the early stages. Treatment is mainly based on controlling cortisol level and reducing tumor burden. High morbidity and mortality accompany this syndrome with sepsis being the leading cause of death due to immunosuppression. In this report, we present three cases with different presentations of paraneoplastic Cushing syndrome as well as a literature review of the diagnostic approach and treatment modalities.

Learning points:
- Learning how to suspect ectopic Cushing syndrome and confirm it among all the causes of excess cortisol.
- Distinguish between occult and severe ectopic Cushing syndrome and etiology.
- Providing the adequate treatment of the primary tumor as well as for the cortisol excess.
- Prognosis depends on the differentiation and type of the primary malignancy.
Case presentation

Case 1

A 46-year-old female patient, who is a smoker (10 pack-years) with a medical history relevant for hyperthyroidism and locally invasive ductal breast cancer treated with mastectomy and chemotherapy, was admitted for generalized fatigue. History goes back to two months prior to presentation when she started complaining of right lower quadrant colicky abdominal pain associated with diarrhea, lethargy and weight gain of 15 kg over one month. On physical examination, our patient was found to have hirsutism grade 3 located mainly in the upper lip, chin and back, with flushing, abdominal purple striae and high blood pressure reaching 220/100 mmHg.

Case 2

A 51-year-old male patient, heavy smoker (more than 30 pack-year), with recent diagnosis of type II diabetes mellitus and hypertension, presented to the hospital with 15 days history of lethargy, fatigue and generalized edema (including arms, face, lips and eyelids). Patient reported weight loss of 14 kg despite his edema with dyspnea on minimal exertion in the last 4 months. On physical examination, abdominal striae and buffalo hump were noted.

Case 3

A 41-year-old male patient, heavy smoker (more than 20 pack-years), obese, with a history of uncontrolled diabetes mellitus type 2 on insulin therapy and glucagon-like peptide-1 receptor agonist, hypertension on angiotensin II receptor antagonist, primary hypothyroidism on hormonal replacement and coronary artery disease, presented for altered general status with anorexia and weight loss of 15 kg since 2 months.

On physical examination, he had right upper quadrant tenderness and bilateral pitting edema on lower limbs with an elevated blood pressure of 170/100 mmHg and hemoglucotest of 278 mg/dL.

Investigation

Case 1

Laboratory data showed severe hypokalemia with a potassium level of 1.6 mg/dL (normal range: 3.5–5.1), hyponatremia of 104 mg/dL (normal range: 135–145) with metabolic alkalosis (bicarbonate of 35 mEq/L, normal range: 22–28).

Magnetic resonance imaging (MRI) of abdomen and pelvis revealed liver and pelvic bone (sacral) lesions compatible with metastasis. Brain MRI revealed metastatic lesion in right frontal region measuring 27 mm in diameter with perilesional edema. Positron emission tomography (PET) scan was performed and showed right lung mass with locoregional lymphatics (Fig. 1), with metastasis to liver (Fig. 2), adrenal glands, skeleton and peritoneal cavity.

Bronchoscopy was done and biopsy pathology revealed undifferentiated small-cell carcinoma of the lung.

In front of such a presentation (high blood pressure, severe hypokalemia, hyponatremia and metabolic alkalosis), supine renin and aldosterone levels were measured and showed respectively 8.1 pg/mL and 40 pg/mL (renin normal range supine level: <20 pg/mL and
aldosterone normal range supine level: 10–105 pg/mL) excluding hyperaldosteronism. 24-h urine collection for metanephrine and catecholamine were unrevealing.

As her clinical presentation raised the suspicion of Cushing syndrome, adrenocorticotropic hormone (ACTH) level was measured and was found to be 201 pg/mL (normal level: 0–46) and 08:00 h serum cortisol was 50 µg/dL (normal level: 10–20). Dexamethasone suppression test was performed with 0.5 mg oral dexamethasone every 6 h for 48 h, then 24-h urine free cortisol level the second day turned to be 5084.7 µg/24 h (4.3–176). Cortisol and ACTH were 26 µg/dL and 185 pg/mL respectively after 8 mg of overnight oral dexamethasone (normal level for ACTH: 0–46 and for cortisol: 10–20), and dehydroepiandrosterone (DHEAS) hormone level was normal 156 µg/dL (normal range: 74.8–410).

A brain MRI confirmed the absence of any pituitary abnormality. Therefore, a diagnosis of ectopic Cushing syndrome was established.

**Case 2**

Laboratory data did not point to any abnormal values except for mild leukocytosis of 13 400 wbc/microliter (normal range: 4500–10 500), hypokalemia of 3.4 mg/dL (normal range: 3.5–5.1) and metabolic alkalosis with a bicarbonate of 35 mEq/L (normal range: 22–28).

Computed tomography (CT) chest showed anterior mediastinal mass. In addition, PET scan revealed irregular band of parenchymal consolidation in the left lung superimposed with interstitial infiltrates extended over medial aspect of upper and lower lobes, encompassing hilar region, in addition to 2 enlarged lymph nodes measuring 32 mm and 31 mm diameters in upper anterior mediastinum that could represent either a chronic inflammatory process or neuroendocrine tumor of the left lung with secondary mediastinal lymph nodes (Fig. 3).

A 24-h urine collection for cortisol was performed in front of these clinical features and confirmed Cushing syndrome with a urine cortisol level of 2761.2 µg/24 h (normal range: 4.3–176). To document ectopic Cushing syndrome, 8 mg dexamethasone was given overnight, and on the second day morning, cortisol and ACTH levels were 29 µg/dL and 133 pg/mL respectively (normal level for ACTH: 0–46 and for cortisol: 10–20).

Patient underwent mediastinal biopsy, and pathology confirmed malignant cells with a poorly differentiated lung cancer compatible with small-cell carcinoma.

**Case 3**

Laboratory tests on admission showed severe hypokalemia of 1.3 mg/dL (normal range: 3.5–5) with hypochloremic metabolic alkalosis with a bicarbonate of 45 mEq/L (normal range: 22–28) and chloride of 79 mEq/L (normal range: 96–106). Despite potassium replacement, his hypokalemia persisted and improved only on aldactone.

Cardiac ultrasound was normal and chest X-ray revealed bilateral pleural effusion. CT of chest and abdomen demonstrated multiple mediastinal lymph nodes, with the most prominent being sub-carinal measuring 3 × 3 cm with a necrotic center, left and right hilar adenopathies of 3.5 and 2.7 cm respectively (Fig. 4), bilateral pleural effusion, mainly on the left, and right hilar adenopathies of 3.5 and 2.7 cm respectively (Fig. 4), bilateral pleural effusion, mainly on the left, and right hilar adenopathies of 3.5 and 2.7 cm respectively (Fig. 5).

**Figure 4**
Multiple mediastinal lymph nodes, the biggest one subcarinal measuring 3 × 3 cm (white arrow), left and right hilar adenopathies on CT of the chest.
inferior lobe consolidations with air bronchogram and multiple liver lesions (Fig. 5).

Subsequently, a PET scan confirmed lymph nodes mainly in the carina and supra-carina, right and left hilum, right paratracheal, upper para-esophageal, right supra-clavicular, right cervical and in the left cervical region compatible with metastasis, liver metastasis with fixation of the tracer mainly in the lumbar spine, pancreas and colon.

CT-guided liver biopsy confirmed poorly differentiated neuroendocrine tumor. Anti-chromogranin and anti-synaptophysin antibodies staining were positive. A workup searching for the primary tumor was started with a gastroscopy and colonoscopy that turned to be unrevealing. Bronchoscopy and lymph node biopsy were negative for malignancy.

In the context of uncontrolled diabetes, hypertension, obesity, hypokalemia and metabolic alkalosis with the evidence of malignancy of unknown origin, 24-h urine for free cortisol was 600 µg/24 h (normal range: 4.3–176).

Dexamethasone test of 8 mg was performed. Morning cortisol and ACTH were not suppressed with values of 24, 8 µg/dL and 134 pg/mL respectively (normal level for ACTH: 0–46 and for cortisol: 10–20).

**Treatment**

**Case 1**

Due to her refractory hypokalemia despite adequate replacement, she was started on aldactone 50 mg twice daily and ketoconazole 600 mg for her hypercortisolemia, chemotherapy with doxorubicin and paclitaxel for her lung cancer, zolendronic acid and radiotherapy for bone and brain metastasis respectively.

**Case 2**

The patient was treated with ketoconazole and then chemotherapy.

**Case 3**

Chemotherapy with carboplatin and etoposide for stage four neuroendocrine tumors was initiated. Everolimus of 10 mg/day and sandostatin 30 mg every one month were also given thereafter.

**Outcome and follow-up**

**Case 1**

She had recurrent hospitalizations for febrile neutropenia and left-sided cerebrovascular accident. Unfortunately, she died 1 year after diagnosis.

**Case 2**

He passed away after several months of the diagnosis.

**Case 3**

He did not receive any therapy for his ectopic Cushing and passed away 1 year after diagnosis.

**Discussion**

Lung cancer is the most leading cause of cancer death worldwide. Several tumor types are classified upon shared neuroendocrine features. These tumors include small-cell lung carcinoma (SCLC), large-cell neuroendocrine carcinoma and carcinoid tumors. SCLC and large-cell neuroendocrine carcinomas are characterized clinically by a more aggressive course and pathologically by a much higher mitotic rate comparing with pulmonary carcinoids.

SCLCs are poorly differentiated, with high-grade, aggressive behavior, representing 15% of all lung cancers, occurring mainly in smokers, with only 1% of these tumors found to be in non-smokers. The incidence is decreasing over the last decades, characterized by rapid doubling time, high growth rate and usually discovered with disseminated disease, but has a good initial sensitivity to chemotherapy.

At the other end, pulmonary carcinoid tumors (PCT) deriving from Kulchitsky cells of bronchial epithelium, constitute 2–5% of lung tumors. 25% are located within the airways and called bronchial carcinoid tumors. They
are a rare group of pulmonary neoplasms, characterized by indolent clinical onset. Typical carcinoids are well differentiated, low grade, slowly growing tumors that rarely metastasize to extrathoracic structures. Atypical carcinoids are of intermediate grade and differentiation (1).

Symptoms may result from local effects of the tumor, from regional or distant extension, or from effects not related to metastases such as paraneoplastic syndromes, due to secretion of various peptides or hormones by malignant cells or secondary to the impact of neoplastic cells antibodies on normal cells, which can precede cancer features (2). Thus, paraneoplastic syndrome can be the presenting diagnosis, but majority of patients are diagnosed at relapse (3).

Around 1–2% of lung neuroendocrine tumors (NET) are associated with Cushing syndrome. Lung NET is the most common cause of ectopic ACTH production.

Tumors can be identified usually with one or more than one syndrome simultaneously (as paraneoplastic ectopic Cushing, syndrome of inappropriate antidiuretic hormone secretion (SIADH), Lambert-Eaton, hypercalcemia, hypercalcitoninemia), especially when arising from a neuroendocrine tumor (4). Many cases reported the presence of 2 paraneoplastic syndromes in SCLC.

Ectopic Cushing syndrome (ECS) is due to hypercortisolism secretion from non-pituitary tumors. Cushing syndrome (CS) may be either ACTH dependent (80%) or ACTH independent (20%). From the ACTH-dependent causes, Cushing disease constitutes the majority (65–70%). Ectopic secretion of ACTH by non-pituitary tumors accounts for 10–15%, whereas ectopic secretion of CRH by non-hypothalamic tumors and factitious CS secondary to exogenous ACTH administration are extremely rare (<1%).

Regarding the ACTH-independent causes, factitious CS is the primary cause, then adrenocortical adenomas and carcinomas, while bilateral adrenal micronodular and macronodular hyperplasias comprise the minority (<1%).

Two-thirds of endogenous elevated cortisol is caused by ACTH-secreting pituitary tumors, 15% by primary adrenal glands and 15% by ectopic paraneoplastic Cushing (5). Differentiation between the latter and Cushing disease is often difficult (6).

ECS affects 10% of cancer patients; 1% of patients with PCT and 4.5% of patients with SCLC (1, 8).

It is the second most common paraneoplastic syndrome in SCLC patients, after SIADH, occurring frequently in those with metastases to adrenal glands with a prevalence of 1–5% due to excess cortisol secretion in this area (7).

ECS is the second most common paraneoplastic syndrome in carcinoid tumors after carcinoid syndrome (8).

ECS occurs mainly in elderly but some cases reported a sporadic form in young population. It is rare, appearing in 50% of cases in lung cancer (30–46% in carcinoid tumors from which 80% are intrabronchial, 8–20% in SCLC and rarely in adenocarcinoma), in addition to thymic neoplasms in 15%, pancreatic neuroendocrine tumors, medullary thyroid cancers, pheochromocytomas and unidentified tumors in 12–19% of cases as in our last case. Less commonly, it is associated with parangliomas, breast, kidney, prostate and esophagus cancer (3, 5, 7).

When arising from SCLC, diagnosis can be difficult especially when it presents without the classical signs of CS, and later due to chemotherapy (7). Final diagnosis is done after resection of the primary tumor and confirmation by histology of the neuroendocrine type or the positivity of ACTH staining.

Presentation can be manifested by clinical symptoms of Cushingoid appearance such as proximal muscle weakness, peripheral edema, abnormal fat distribution, moon face, buffalo neck, acne, striae and more commonly by electrolytes disturbance such as hypokalemia and metabolic alkalosis. Severe hypertension, hyperglycemia and even hyperosmolar hyperglycemic state (HHS) may be the first manifestations of ECS and underlying malignancy (9).

Symptoms may be mild or severe proportionally to the cortisol level and not to the tumor size or duration of exposure (10). All the cases discussed here presented with refractory hypertension, hypokalemia and one with uncontrolled diabetes. Two patients out of three of our cases have clinical Cushingoid features: the first one developed facial hirsutism, weight gain and abdominal striae. The second one presented with buffalo hump and generalized edema. In the first case, 24-h urine cortisol was much higher than the 2 other cases, explaining the weight gain typical of CS, while in 2 other cases, weight loss was probably due to the predominance of the tumor despite the presence of some Cushingoid symptoms in the second case.

Bronchial carcinoid tumors have slow onset of symptoms, thus at presentation, Cushingoid features are already established (11).

SCLC associated with ECS has the worst prognosis because of several features related to the disease itself like advance stage, poor response to chemotherapy in addition to consequences of the paraneoplastic syndrome as increased susceptibility to infections (opportunistic
infections and sepsis) due to the immunosuppressive effect and increased thromboembolic events due to the hypercoagulable state (7).

Patients with SCLC can live 3–6 months; therefore, early diagnosis is challenging. The 3 patients died early after the diagnosis; 2 with documented SCLC, and the third one has poorly differentiated neuroendocrine tumor probably due to SCLC.

Excellent prognosis is seen in typical carcinoid tumors with a 5-year survival rate of 87–100%, 10-year survival rate of 82–87% and 3% recurrence rate after operation, whereas atypical carcinoid tumors have much lower survival rate and higher recurrence rate (12).

The diagnosis is usually set by clinical characteristics of Cushing and underlying malignancy, serum cortisol (>550 nmol/L), 24-h urine cortisol (>300 nmol/L) and ACTH level (>15 pmol/L) in addition to dexamethasone suppression test if necessary (3). Ectopic ACTH secretion is more common in high-grade neuroendocrine tumors (SCLC) than in low-grade neuroendocrine tumors (CT). These tumors secrete a large concentration of ACTH, by direct release or production of precursors (8).

Further differentiation with other forms of hypercortisolemia like Cushing disease is performed by pituitary MRI (20–30% of adenomas are not visible), if revealing, or high-dose dexamethasone and corticotrophin-releasing factor (CRF) stimulation tests. ECS is not responsive to these 2 tests (2, 5). Serum and urinary cortisol levels in ECS are not suppressed to a level <5 µg/dL after 8 mg dexamethasone overnight and after 0.5 mg every 6 h for 8 doses respectively, like our cases. Similar results after administration of CRH confirmed ECS. However, 20% of Cushing disease cases also do not respond to high dose of dexamethasone and 30–40% of ectopic cortisolism in bronchial neuroendocrine tumors is suppressed with this test, making CRF test more specific. Many studies favored combination of these 2 tests in addition to tumor markers like calcitonin, chromogranin, beta-HCG, catecholamines, alpha-subunit, for accurate diagnosis. All carcinoid tumors synthesize neuropeptides such as synaptophysin, neuron-specific enolase (NSE) and chromogranins, identified by immunohistochemical markers (13).

Measurement of DHEAS is sometimes useful as it is decreased in adrenal Cushing and normal or high in ACTH-dependent Cushing.

ECS affects females as well as males equally, whereas Cushing disease affects more young female (14).

The gold standard diagnosis, inferior petrosal sinus sampling (IPSS), that demonstrate gradient in ACTH concentration between the affected side sinus and the periphery in pituitary lesions whereas absence of this gradient in ECS, but it is not performed in most cases, because it is an invasive procedure of bilateral catheterization of the femoral vein up to the petrosal sinuses under fluoroscopic guidance, carrying severe neurological accidents (11).

21 and 26% of patients with ECS have false-positive responses to dexamethasone and/or CRH stimulation tests, and IPSS has a sensitivity of 88–100% and a specificity of 90–100% in identifying ectopic tumors (11).

In 12–19% of cases, the usual imaging fails to show any tumor as a cause of ectopic ACTH secretion and tumors may appear later after several years of ECS diagnosis (11). Therefore, specific imaging is often required, probably because of the small tumor size and the difficulty in tumor localization. CT and MRI of chest for lung cancer, CT abdomen with gastroscopy and colonoscopy for gastrointestinal tumors and thyroid ultrasound for thyroid cancer are useless for identifying ectopic ACTH-secreting tumor.

Typical carcinoid tumors have high concentration of somatostatin receptors. Octreotide test can be useful (14). Octreotide binds to SSTR-2 and SSTR-5 with high affinity. The expression of SSTR in bronchial carcinoid tumors has not been investigated (13).

This test has a sensitivity of 57% and positive predictive value of 79% and failed to identify tumors with negative somatostatin receptors (13).

FDG-PET scan identifies small metabolically active lesions with a sensitivity of 64% and positive predictive value of 53% for occult disease, as well as F-Fluorine-18-dideoxy-phenylalanine (F-DOPA) PET scan which is more appropriate for later stages in undifferentiated neuroendocrine tumors (6, 14). Our last case failed to show the primary tumor origin and other imaging’s are unavailable in our institution.

When localization of the ACTH-secreting site failed, it suggested pulmonary carcinoid tumor (12).

Carcinoid tumors are very small, slow growing, highly vascularized, they can be confused with pulmonary vessels. CT and MRI failed to detect these tumors in 50% of cases. Other tests such as high resolution CT, scintigraphy, or PET scan can be used.

Another important cause of failed localization of these tumors is low diagnostic importance of bronchial brushings; tumor cells are small, they are unable to exfoliate because of the lining of intact bronchial mucosa, making broncoscopy with bronchial brushings difficult to reach them (12).
Medullary thyroid cancers and pancreatic islet tumors are large and metastasized to liver by the time ECS is discovered (11).

When imaging’s failed to localize tumors, signs and symptoms are present and associated with a worse prognosis (13).

In paraneoplastic CS, malignancy is usually more extensive (discovered with 2 or more metastatic sites) with reduced response to first-line chemotherapy, excessive weight loss, reduced performance score and more susceptibility to infections. Administration of chemotherapy in the setting of immunosuppressive state induced by hypercortisolism, cancerous background, and metabolic disorders caused by electrolyte disturbance and hyperglycemia, aggravate the condition and can also be life threatening. Thus, initiation of palliative approach can be sometimes reasonable. Sepsis can be the primary complication and cause of death (3).

Surgical resection of the primary tumor with lymphadenectomy is beneficial when performed for localized tumors, but it is often impossible in the advanced setting (4, 14).

Surgery is curative in >80% of patients, when performed (1).

Small typical carcinoid tumors are resected with mediastinal lymph nodes dissection; whereas atypical carcinoid tumors require lobectomy or even pneumonectomy with a regular follow-up by history, physical exam or imaging’s every 6 months for 2 years then yearly.

In cases when localization of primary tumors cannot be achieved, treatment of hypercortisolemia is essential with follow-up imaging’s to detect and resect tumors.

Treatment of hypercortisolemia can be achieved either medically or surgically by adrenalectomy (12).

Less than 15% of well-differentiated carcinoid tumors presented with metastases. 5-year survival rates are usually >90% (1).

The important issue in treatment is controlling high cortisol level before initiating systemic chemotherapy for both better survival and prevention of complications such as sepsis triggered by steroid immunosuppression and agranulocytosis induced by chemotherapy. Decreasing cortisol can be achieved by ketoconazole, metyrapone, etomidate, mitotane and mifepristone (7).

Ketoconazole is a cytochrome P450 3A4 inhibitor that inhibits 11-beta hydroxylase and 17-hydroxylase necessary from steroidogenesis. It has a rapid onset of action but can increase the toxicity of chemotherapy, impair response to stress and induce hypogonadism. Liver function tests should also be closely monitored because of liver failure risk (10).

Mitotane, in addition to decreasing cortisol level, has a cytotoxic effect on adrenal glands, a delayed onset of action and often intolerance due to gastroenterologic and neurologic side effects. It is reserved for second-line treatment (14).

Metyrapone blocks cortisol and aldosterone synthesis, with accumulation of androgens leading to hirsutism and mineralocorticoid precursors exacerbating hypokalemia, edema and hypertension (10).

Etomidate, an intravenous drug, is reserved for severe cases. Mifepristone decreases cortisol action on receptor (10).

Combination therapy of steroidogenesis inhibitors such as ketoconazole, metyrapone, etomidate and mitotane with dual or triple therapy can be used if control cannot be established by monotherapy (7). Glucocorticoid receptor antagonist like mifepristone can be used as well. Cyproheptadine, bromocriptine, somatostatin and valproic acid are neuromodulators of CRH and ACTH synthesis. Response to this kind of treatment is generally poor. Side effects include postural hypotension, weight gain, sedation and hepatotoxicity (8).

First-line chemotherapy for SCLC is platinum–etoposide combination. Failure of initial treatment, extension of the primary tumor, poor performance status and lack of sensitivity to the first chemotherapy regimen point to initiation of palliative care as paraneoplastic CS is indicative of poor survival in the majority of SCLC cases (3).

Our third patient was treated with carboplatin and etoposide then with everolimus, sandostatin for treatment of patients with progressive neuroendocrine tumors. Combination of everolimus and sandostatin showed a clinically significant improvement in functional neuroendocrine tumors.

Bilateral adrenalectomy can be performed as a last resort if life-threatening complications emerge. Done laparoscopically, it carries low mortality and morbidity with a successful rate of 100% if done by expert surgeons in non-critically ill patients, especially if there is severe hypercortisolism altering prognosis and ineffective medical treatment (6, 14).

Paraneoplastic syndrome with active hormone secretion can be used as a tumor marker and for follow-up, before and after initiation of treatment (4).

Prognosis depends on cortisol level and tumor type. High cortisol level in association with SCLC, thymic and medullary thyroid tumors has the worst prognosis (10).
Patients with SLCL have the worst prognosis dying within 12 months of diagnosis; patients with bronchial carcinoids have the best prognosis (11).

Conclusion
Paraneoplastic syndromes require high clinical suspicion for early diagnosis and prompt management for improving outcomes and can be the first manifestation of malignancy. Based on the above cases, paraneoplastic CS should be considered in the differential diagnosis of any patient presenting with the phenotype of CS, hypertension, hyperglycemia, electrolytes disturbance, with or without underlying cancer, especially that the primary tumor could be still unidentified at the time of diagnosis.

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All patients are dead and consent could not be obtained before their death.

Author contribution statement
Dr Carine Ghassan Richa (fellow of endocrinology in the Lebanese University, who writes this article). Primary care physician of the patient 1 and 3: Dr Fadii Nasr (Oncologist at Mount Lebanon hospital who has managed these patients oncoology-wise with the chemotherapy). Consulted physicians of the patients 1 and 3: Dr Marie Merheb and Dr Elie Gharios (endocrinologists at Mount Lebanon hospital, Dr Merheb has critically revised this manuscript and gives final approval of the version). Primary care physician of the patient 2: Dr Georges Halabi (endocrinologist at Mount Lebanon hospital). Dr Khadija Jamal Saad (fellow of endocrinology in the Lebanese University, who participates in drafting this manuscript).

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