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Paraneoplastic Cushing's syndrome in a patient with small cell lung cancer: case report

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ABSTRACT

We discuss the case of small-cell lung cancer patient with clinical features of paraneoplastic Cushing's syndrome. The primary symptoms included electrolyte imbalance, glucose intolerance, and increased oedemas of the lower extremities. In January 2016, the patient's performance status was 2 in ECOG scale and antineoplastic treatment with carboplatin and etoposide was initiated. Following the 2nd chemotherapy cycle symptoms of paraneoplastic syndrome significantly were alleviated and performance status improved (grade 1), allowing a change of chemotherapy protocol to a more standard one (cisplatin and etoposide). At the time of the subsequent chemotherapy cycles the patient's good general condition was maintained. Use of causative treatment allowed achievement of significant clinical improvement and recovery of laboratory values.

Key words: small-cell lung cancer, paraneoplastic syndrome, Cushing's syndrome

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Introduction

Paraneoplastic syndrome is a clinical condition related to malignancy but not directly resulting from local tumour burden or distant metastases. The symptoms of paraneoplastic syndrome could precede other clinical features of the cancer. There are two basic mechanisms of development of paraneoplastic syndromes: the first is associated with hormones and cytokines produced by neoplastic cells, and the second results from the activity of antibodies produced against cancer cells that have an impact on healthy tissues [1, 2].

The incidence of paraneoplastic syndromes is relatively high, and they affect approximately 10% of cancer patients [1]. The prevalence depends on the type and stage of cancer. Although very rare, paraneoplastic Cushing's syndrome results from ectopic production of adrenocorticotrophic hormone (ACTH). It affects 1–5% of all patients with diagnosis of Cushing's syndrome [3]. In approximately half of cases this syndrome is diagnosed in patients with small-cell lung cancer or neuroendocrine cancers of the respiratory tract [2–4].

The syndrome of ectopic ACTH release is also seen in patients with thymic neoplasms, pheochromocytoma, and medullary thyroid cancer [1, 3].

In the presented paper we discuss a history of female patient with paraneoplastic Cushing's syndrome in the course of small-cell lung cancer.

Case report

A 58-year-old female patient with stage IV small-cell lung cancer was admitted in January 2016 to the Clinic of Chemotherapy of the Oncology Department at the Medical University of Łódź. Her performance status was assessed as 2 in the ECOG (Eastern Cooperative Oncology Group) Scale, with dyspnoea at rest and severe oedemas of the lower extremities. The patient had a long medical history of many concomitant diseases (type 2 diabetes, hypertension grade 2, and hyperthyreosis after treatment with radioactive iodine in 2013), mitral

insufficiency, and tricuspid regurgitation. She was an ex-smoker with 35 pack-years in her history.

The current disease was diagnosed in October 2015. At this time the patient was not qualified for elective operation of total vaginal and uterine prolapse due to hyperthyreosis. Further diagnostic tests were planned; however, the patient was discharged at her request, against medical advice.

In November 2015 the patient was hospitalised in internal medicine department of regional hospital due to reduced exercise tolerance, heart palpitations, progressive oedema of the lower extremities, and increased of abdominal circumference. Significant hyperglycaemia was revealed in laboratory tests. Type 2 diabetes was diagnosed and insulin treatment introduced. Chest X-ray and abdominal ultrasound (USG) were performed, and then the diagnostics were upgraded by chest computed tomography (CT), which revealed a tumour of the right lung, a pancreatic tumour, and a tumour of left suprarenal gland (probably metastatic). The patient was discharged with the recommendation to urgently contact an oncology specialist.

Fine-needle aspiration of the pancreatic mass was performed in December 2015. Additional bronchoscopy was planned, but the patient withdrew consent. Due to ambiguous results of cytology (neuroendocrine cancer cells present) oligobiopsy of the tumour was performed. Oligobiopsy of pancreas can not be considered as a routine test, however, low-differentiated small-cell cancer of most probable lung origin was diagnosed (Ki67 index — 100%).

In January 2016 the patient was re-hospitalised in the Emergency Department of Nicolaus Copernicus Regional Specialist Hospital in Łódź due to significant worsening of general health, progressive dyspnoea at rest with chest tightness and lower extremities oedema, as well as low urine output. Laboratory tests revealed marked hypokalaemia (3.0 mmol/L). The patient was referred to the Palliative Care Unit, where supportive treatment was administered with improvement of general condition. The patient was referred to the Clinic of Chemotherapy of the Oncology Department for urgent introduction of causative treatment.

At the time of admission to the clinic physical evaluation revealed features of superior vena cava syndrome (widened neck outline, enlarged veins on the left side of the chest), exophthalmos, soft package of lymph nodes in the left supraclavicular area, and pasty oedema of lower extremities up to the level of knee joints). Respiratory murmurs over the right lung were significantly weakened. The abdomen was raised above chest level, and during palpation it was soft, painless, and without pathological mass. Due to Cushingoid posture (visceral obesity), round face shape, and numerous claret-coloured stretch marks on the skin, a diagnosis of Cushing's syndrome was considered for the first time.

Laboratory tests revealed hypokalaemia (2.8 mmol/L) and lymphopaenia ($1.09 \times 10^3/\mu\text{L}$). Serum ACTH and neurospecific enolase (NSE) concentration was additionally evaluated, and the values were significantly increased [173.0 pg/mL (normal range 7.9–66.1 pg/mL) and 720 $\mu\text{g/mL}$ (normal range 16.3 $\mu\text{g/mL}$), respectively].

Due to clinical symptoms and increased ACTH serum concentration, paraneoplastic Cushing's syndrome was diagnosed. Taking into consideration the significant dynamics of cancer and the demand for quick introduction of causative treatment, no additional tests to confirm ectopic release of ACTH were performed (provocative test after administration of 8 mg of dexamethasone, octreotide test).

Due to hyperthyreosis CT scans with contrast in order to assess the current clinical stage of disease were temporarily deferred. However, chest X-ray and abdominal USG revealed abnormalities — abnormal mass localised in front of right lung hilus (40 mm and 26 mm in diameter, respectively), widening of right superior mediastinum with modelling of trachea to left side, vestigial effusion in interlobular fissures, enlargement of the cardiac silhouette, tuberos, hypoechoic, solid change with the size 98 × 54 × 60 mm in the area of the tail of the pancreas and tumour of left suprarenal gland with the size of 86 × 50 mm.

Supportive management was immediately introduced (including potassium supplementation, diuretics, eplerenone, chlorthalidone, propranolol), and insulin therapy was continued. After achieving normokalaemia therapy with digoxin was added.

Due to the presence of a mediastinal mass affecting systemic haemodynamics as well as the need for restricted fluid supply, systemic treatment with carboplatin and etoposide was started, with the intention of changing to cisplatin after improvement of the patient's general state.

At chemotherapy cycle 2, the patient's performance status was remarkably better (ECOG 1), with no dyspnoea at rest and small oedema of the lower extremities. The treatment was changed to typical protocol (cisplatin and etoposide).

At chemotherapy cycle 4, the patient's performance status was still good (ECOG 1), without dyspnoea or oedema of the lower extremities. Serum potassium concentration was within normal range, and ACTH and NSE concentrations normalised (64.9 pg/mL and 12.3 $\mu\text{g/mL}$, respectively). Repeated chest X-ray revealed complete response of tumour mass previously located in front of the right hilus and partial remission of the mediastinal mass, with no increased heart silhouette. Abdominal USG revealed partial remission of the tumour mass in the pancreatic tail and left suprarenal gland.

Systemic treatment was terminated after six chemotherapy cycles. Good performance status was maintained, similarly to normalisation of laboratory values and partial remission in imaging evaluations. The patient did not

agreed to have elective brain irradiation and failed to attend an appointed follow-up visit in the oncology outpatient clinic. The subsequent fate of the patient is unknown.

Discussion

Paraneoplastic Cushing's syndrome affects 1–5% of patients with SCLC [2–4]. In a retrospective trial, Nagy-Mignotte et al. indicated that intercurrent ectopic release of ACTH in patients with SCLC is associated with more advanced clinical stage, poor response to systemic treatment, and shortened overall survival [4]. The reasons for poorer prognosis include reduced chemosensitivity, higher clinical stage, as well as higher infection risk (among others, opportunistic infections and sepsis resulting from hypercortisolaemia) [1, 3, 4]. Accordingly, normalisation of cortisol concentration before systemic treatment is advised. In order to reduce hypercortisolaemia, steroidogenesis inhibitors and corticosteroids agonists (e.g. ketoconazole, mitotane, aminoglutetymide, and metapyrone) are used [1–4].

Paraneoplastic Cushing's syndrome could be distinguished from classic Cushing's syndrome and increased pituitary release of ACTH (Cushing's disease) based on serum cortisol and ACTH concentration and brain CT (exclusion of pituitary tumours). The laboratory tests performed in order to assess this condition include a provocative test after 8 mg of dexamethasone (oral dexamethasone 2 mg every six hours for two days — measurement of cortisol concentration in daily urine collection at baseline and on the 2. day of dexamethasone administration) as well as octreotide test [1, 3, 4]. Corticotropin releasing factor (CRF)-stimulation test could also be performed; however, its specificity is not 100% due to the sensitivity of some ectopic tumours producing ACTH to CRF. In cases of ectopic ACTH production cortisol is not suppressed due to continuous release of adrenocorticotrophic hormone.

Cushing's syndrome due to the increased ACTH production could result in increased blood pressure, hyperpigmentation of the skin, mental disorders, oedemas, glucose intolerance, abnormal fat tissue dis-

tribution, stretch marks on the skin, muscle weakness, and hypokalaemia alkalosis [1]. The main symptoms of paraneoplastic Cushing's syndrome include electrolytic disturbances rather than morphological features of that syndrome because hypercortisolaemia is an acute state, and the patient survival time is too short to develop morphological changes [3]. This is very important in patients with suspected Cushing's syndrome, to determine the source of ACTH release based on the aforementioned tests. Similarly to other endocrinology paraneoplastic syndromes, a characteristic feature of ectopic ACTH release is improvement of hormonal state and alleviation of symptoms during antineoplastic treatment [2]. Management is based on control of hypercortisolaemia and metabolic complications as well as proper antineoplastic therapy.

Summary

The presented patient was diagnosed with paraneoplastic Cushing's syndrome based on characteristic clinical signs and symptoms (morphological features, increased ACTH serum activity, hyperglycaemia, hypokalaemia, lymphopaenia) and the presence of a typical picture of underlying malignancy. No additional endocrine-related tests were performed to confirm ectopic release of ACTH. Proper supportive care together with active antineoplastic treatment led to considerable improvement of the patient's general condition, partial cancer response, and normalisation of endocrine functions.

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