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CASE REPORT

A case of recurrent non-small-cell lung carcinoma and paraneoplastic Cushing's syndrome

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Summary Secretion of ectopic adrenocorticotropic hormone (ACTH) with consequently Cushing's syndrome is a rare paraneoplastic phenomenon. It has been described in a variety of malignancies, like bronchial carcinoids, small-cell lung carcinoma, thymoma, pancreatic carcinoma and other. In many cases of suspected ectopic ACTH secretion, it is difficult to histologically or cytochemically confirm the diagnosis. We present a 63-year-old woman with a recurrent poorly differentiated squamous cell lung carcinoma with clinical and biochemical features consistent with ectopic Cushing's syndrome. Immunocytochemical staining confirmed the secretion of ACTH by tumour cells.

1. Introduction

''The name of Harvey Cushing (1869—1939) was immortalized in the history of medicine, by his discovery, in 1912, of Cushing's disease, an endocrine syndrome caused by a malfunction of the pituitary gland. This discovery was described in detail in: The Pituitary Body and its Disorders [1].''

Cushing's syndrome is characterized by truncal obesity, a 'buffalo hump' and/or 'moon face', purplish abdominal striae, ecchymoses and proximal myopathy, accompanied by non-specific symptoms like edema, hypertension, fatigability and weakness, hirsutism, hyperpigmentation and diabetes. The syndrome can be ACTH-independent due to autonomous glucocorticoid-secreting adrenocortical adenomas or carcinomas. However, in most cases Cushing's syndrome is ACTH-dependent. The aetiology is bilateral adrenal hyperplasia due to hypersecretion of pituitary ACTH or ectopic production of ACTH by a non-pituitary cause like malignancy, respectively called Cushing's disease and

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Cushing's syndrome. Numerous tumours have been reported to secrete ACTH, like bronchial carcinoids, thymoma, pancreatic malignancy and small-cell lung carcinomas (SCLC).

We present a patient with a previous history of non-small-cell lung carcinoma (NSCLC), typical features consistent with Cushing's syndrome and mediastinal lymphadenopathy on computerized tomography (CT).

2. Case report

In March 2005, a 63-year-old woman presented in our hospital with progressive dyspnea. She had a history of previous poorly differentiated squamous cell lung carcinoma of the lower right lobe in June 2001. For this, she had a lobectomy in another hospital with pathological tumour-staging pT1N0M0. After the operation she had gradually gained 50 kg of weight, which she ascribed to cessation of smoking. In January 2005, the general practitioner diagnosed her with hypertension and diabetes.

At presentation, physical findings showed a Cushingoid appearance, with a moon face, buffalo hump and centripetal obesity. There were no signs of hirsutism or hyperpigmentation, nor where there abdominal striae or ecchymoses. There was pitting edema of the legs and some tachypnea. Blood pressure was elevated (RR 175/75 mmHg). Her medication included a potassium sparing diuretic combined with a loop diuretic to control hypertension and edema, a biguanide to control glucose-levels and inhalation-corticosteroids.

Initial laboratory evaluation revealed a severe hypokalemia (K^+ 1.8 mmol/l, Ref. range 3.5—5.0) with normal sodium, magnesium and calcium-levels and a normal renal function. Arterial blood gas analysis revealed a metabolic alkalosis with hypoxemia (pH 7.60; BE 17.1; HCO^{3-} 41.1 mmol/l (Ref. range 22—29), pO_2 53.6 mmHg (7.15 kPa) and pCO_2 40.0 mmHg (5.33 kPa)).

She was treated with intravenous and oral potassium chloride and supplemental oxygen. The diuretics were temporarily discontinued, however a potassium-sparing diuretic had to be re-started because of increasing edema of the legs. Hypertension was treated by an angiotensin I-blocker, utilizing its potassium-sparing quality.

Further investigations revealed high 09:00 h plasma cortisol (1.58 μmol/l, Ref. range 0.18—0.72) with loss of diurnal variation (midnight plasma cortisol 1.43 μmol/l, Ref. range <0.21). Urinary free cortisol was also elevated (12.16 μmol/24 h, Ref. range 0.03—0.28 μmol/24 h), and so were the plasma ACTH-level (223 ng/l, Ref. range 7—50) and plasma renin activity level (6.70 ng/ml/h, Ref. range 0.8—5.5). Serum cortisol failed to suppress following 1 mg dexamethasone overnight (09:00 h cortisol 1.55 μmol/l, Ref. range <0.14). Magnetic resonance imaging (MRI) did not reveal adenomas of the pituitary gland, suggesting that our patient had ectopic ACTH syndrome (EAS).

To identify the source of the ectopic ACTH-production while considering her previous history of a lung carcinoma, a thoracic CT-scan was made, which showed mediastinal lymphadenopathy. On the abdominal CT-scan, there were no signs of adrenal hyperplasia or adenoma. Subsequently bronchoscopy was performed which did not reveal abnormalities. Curved linear endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) was performed to biopsy the enlarged lymph nodes and cytological examination demonstrated poorly differentiated squamous cell carcinoma. Assuming the prior resected tumour in the lower right lobe to be the primary tumour, this lymph node can be regarded as N3. Immuno-cytochemical staining of this specimen was positive for the neuroendocrine marker CD56 and for ACTH, suggesting paraneoplastic Cushing's syndrome (Fig. 1).

The patient was treated with ketoconazole (400 mg three times daily) and plasma cortisol levels decreased, as did the potassium-suppletion needed. She developed bacteraemia with Staphylococcus Aureus-species, originating from a contaminated intravenous catheter. After two weeks of antibiotic treatment, induction-chemotherapy for TxN3M0 NSCLC was administered (Vinorelbin 25 mg/m^2 and Cisplatin 80 mg/m^2). Ten days later, she developed bilateral pulmonary embolisms for which low molecular weight heparin (LMWH) was started. The patient deceased 18 days after onset of chemotherapy. Post-mortem autopsy revealed multiple bilateral pulmonary embolisms as direct cause of death.

3. Discussion

In ACTH-dependent Cushing's syndrome 20—25% of cases are caused by ectopic ACTH syndrome (EAS). It is well known that several lung tumours like bronchial carcinoids and small cell lung carcinoma are associated with EAS in approximately 1—5% of cases [2,3]. In recent literature, bronchial carcinoids seem to be the predominant cause of EAS, while the incidence of SCLC associated with EAS seems to decrease [9]. A possible explanation for this might be the declining incidence of SCLC, apart